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## The newest progress of research on acute trauma-induced coagulopathy

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### ABSTRACT

Traumatic injury remains the leading cause of death with bleeding in the world, representing the main cause of preventable death. But if immediate management could be applied, the outcomes will be dramatically improved. Trauma-induced coagulopathy (TIC) as an early endogenous process in many traumatic patients is driven by the multi-tissue injury and shock, and is associated with increased mortality and bad outcomes in the multi-trauma patients. The understanding of the mechanisms of TIC and its effect on the outcomes of severely injured patients has been developed over the past few years. Here, we aim to review the current understanding and recent findings in the pathobiology of coagulopathy. The principal causes of TIC are hypoperfusion, inflammation response and the activation of the neurohumoral system. Hypoperfusion causes the activation of many biomarkers, like protein C, syndecan-1, plasminogen, and so on. The elevation of these markers indicates the damage of the endothelium, which will lead to autoheparinization in body. When accompanied with acidosis, hypothermia, and hemodilution, the mortality of trauma patients will rise significantly. This article aims to focus on our updated acknowledges on the principal mechanisms and causes of the TIC.

## 1. Introduction

Trauma is a major cause of deaths and is a global health issue, causing about 4 million deaths a year<sup>[1]</sup>. Most potentially preventable deaths are due to blood loss. A lot of patients with multi-trauma develop an early trauma-induced coagulopathy (TIC) (also called acute traumatic coagulopathy, acute endogenous coagulopathy or acute coagulopathy of traumatic shock). Immediate management is essential and will improve the outcomes<sup>[2]</sup>. But the pathophysiologic mechanisms leading to TIC remain unknown. The discovery of TIC stems from the findings including a prolonged prothrombin time (PT) and/or activated partial thromboplastin time (APTT) and/or international normalized ratio (INR) at hospital admission before the resuscitation that are associated with a three-fold to four-fold higher mortality rate and are independently associated with more transfusion needs, organ dysfunction, inflammatory complication and intensive care unit length of stay.

The changes of the coagulation function in the severe traumatic patients are detectable in the early stage of injury, which support the hypothesis of an early endogenous process<sup>[3]</sup>. What we have known is that the TIC is driven by the combination of tissue trauma and systemic hypoperfusion which will activate the neurohumoral system and release catecholamines, resulting in endothelium damage that will immediately and concurrently activate and/or influence many pathways including the vascular endothelium, the coagulation, and natural anticoagulation pathway; it will also affect profibrinolytic, antifibrinolytic, and inflammatory systems. At last, the TIC will happen<sup>[1]</sup>.

As we known, coagulation is an integral part of the innate immune system and the activation of protein C (PC) in the endothelium system seems to be a core mechanism of TIC<sup>[4–6]</sup>, which is one of the post-traumatic inflammatory responses. If the hemorrhage still continues, doctors will infuse crystalloids or hypocoagulable blood products, like lactate ringers and red blood cells, and these fluids will cause hemodilution of the coagulation factors, together with acidemia, consumption of clotting factors and hypothermia and the coagulation function will worsen, and TIC will occur<sup>[5,7,8]</sup>.

Previous studies of TIC were focused on the fluid resuscitation phase (plasma, circulating blood). Recently, many studies are focused on a systemic pathophysiology<sup>[9]</sup>. In the following,

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we will talk about the updated pathophysiologic mechanisms of TIC.

## 2. Defining of TIC

TIC means the derangement of coagulation function due to the tissue hypoperfusion in the severe injured patients caused by major trauma. It is a pathophysiologic response to the tissue injury<sup>[10]</sup>. TIC can be defined by the change of the clotting time and clot strength and also can be recognized by the prolonged PT and/or APTT, and/or INR at hospital admission<sup>[5,10]</sup>. However, we can't just judge the clinically relevant bleeding simply and equate it to the abnormal laboratory values. When the true coagulopathic bleeding happens, it is always uncontrolled, and not only restricts to the injury sites but also becomes diffuse hemorrhage soon. Patients will die rapidly. Distinguishing coagulopathic bleeding at the bedside by clinical doctors is mainly based on our understanding of TIC and we need not only careful observation but also point-to-care test methods. However, there is an effective measure which can help doctors to conclude the epidemiologic view of the prevalence of TIC. Although we are not clearly understanding the mechanisms of TIC, we have already found some clues, like platelet dysfunction, endothelial activation, endogenous anticoagulation, fibrinogen modifications, and hyperfibrinolysis in the progress of TIC<sup>[11]</sup>. The following review will describe the updated articles about the TIC.

## 3. Endothelial injury

There is the endothelial glycocalyx on the surface of the endothelium. The endothelial glycocalyx represents a large structure within the hemostatic system (in adults containing approximately 1 L noncirculating plasma accounting for about 25% of the total intravascular volume) that contains significant amounts of heparin-like substances<sup>[12]</sup>. Degradation may induce endogenous autoheparinization in critical ill patients<sup>[13]</sup>.

As far as we know, when traumatic tissue injury occurs, the neurohumoral system will be activated immediately and our body will release a large amounts of catecholamines leading to redistribution of our blood flow, hemoconcentration and platelet mobilization, then the endothelium will be activated and release procoagulant and profibrinolytic factors<sup>[14–16]</sup>. Although the sympathoadrenal “fight-or-flight” response has been mostly adapted, it may also develop to be maladaptive and at last contribute to organ damage<sup>[9,17]</sup>. When the concentration of catecholamine is high, it may directly damage the endothelium, which will cause local tissue edema, swelling of endothelial cells, cell necrosis and cell de-endothelialization<sup>[18–21]</sup>. The downstream effects of released damage associated molecular patterns will trigger an acute inflammatory response and will cause cell damage<sup>[22–24]</sup>.

## 4. Endothelial glycocalyx

The endothelial glycocalyx laid on the endothelial surface is composed of glycosaminoglycans and proteoglycans. The glycosaminoglycans commonly include heparin sulfates, hyaluronan and chondroitin sulfates. Proteoglycans usually carry heparin sulfates and chondroitin sulfates which are called syndecans. The endothelial glycocalyx plays an important role, limits protein and other soluble substance in the blood entering

the cell junction and regulates cell adhesion and factors recognition, like leukocyte and platelet interaction<sup>[11,25]</sup>. The endothelial glycocalyx also affects the local inflammatory response and the heparin sulfate component which regulates the local cell surface coagulation system.

Syndecans are the most studied glycocalyx. Syndecan family is comprised of four members (syndecan 1–4) and syndecan-1 is thought to be related to trauma and is a transmembrane heparin sulfate proteoglycan with a large extracellular domain and a highly conserved cytoplasmic domain. It is also abundant on the surface of almost all endothelial cells. Each syndecan has its unique cytoplasmic domain. The base function of syndecan-1 is as an integral membrane protein and syndecan-1 can participate in cell proliferation, cell migration and cell-matrix interactions via its receptor for extracellular matrix proteins<sup>[26]</sup>. In the recent research, syndecan-1 is highly regulated during wound repair<sup>[27]</sup>. There is a study demonstrated that as a marker of endothelial glycocalyx degradation in trauma patients, a high level of syndecan-1 on admission is associated with high sympathoadrenal activity and will lead to increase in mortality. Furthermore, patients whose blood contains high level of syndecan-1 are associated with increased tissue and endothelial damage, inflammation response and also with lower PC level, hyperfibrinolysis and prolonged APTT<sup>[27]</sup>.

## 5. PC pathway

As we have mentioned, the degradation of the glycocalyx and tissue hypoperfusion will cause early depletion of PC, the increase of plasma thrombomodulin level and the decrease of factor V level<sup>[7]</sup>. Many studies suggest that the main principal of TIC is the activation of the PC (aPC) pathway. When hypoperfusion occurs, the endothelial tissue will be damaged combined with the degradation of the glycocalyx and the PC will be activated<sup>[28–31]</sup>. PC is a vitamin K-dependent glycoprotein. In normal person, it circulates in the plasma; when thrombin bond to its receptor, which is called the endothelial PC receptor (EPCR), the PC will be activated. Then, the PC will combine with the transmembrane glycoprotein and we call it as thrombin-TM complex<sup>[30]</sup>. The formation of the thrombin-TM complex will further enhance the aPC. Once it is activated, PC has a double anticoagulant actions and at last it will lead to TIC through the following mechanisms: (1) acting as cofactors in the activation of factors X and II, it inhibits the extrinsic coagulation pathway by proteolytical cleaving of the peptide which bonds in activated procoagulant factors V and VIII<sup>[6]</sup>; (2) it inhibits plasminogen activator inhibitor-1 (PAI-1) and promotes fibrinolysis, and it also can reduce inflammation response by binding the protease-activated receptors-1 to EPCR and decreasing leukocyte nuclear factor κB activation<sup>[32]</sup>. At last, aPC can cleave extracellular histones<sup>[33,34]</sup>. Cofactor protein S can also increase the activity of the aPC. Protein S and other factors regulate the tenase complex and this complex can inactivate the factor VIII. Protein S also regulates the prothrombinase complex, which cause the inactivation of factor V<sup>[6]</sup>.

Totally speaking, low PC and high TM complex level are related to poor outcomes among severe injured patients. These patients are more likely to suffer from hypoperfusion and low PC is also related to prolongation of PT, APTT, and hyperfibrinolysis, in which the levels of PAI-1 is low. Some studies use aPC–PC ratio to demonstrate the level of aPC, and reflect the

depression of the fibrinolysis<sup>[35]</sup>. So PC seems to have a complicated role affecting the pathway of coagulation in trauma or shock patient. However, the exact mechanisms of PC pathway activation are still needed to be verified, such as the mechanism of triggering, the activation of PC and other regulatory factor. Most recent studies focus on the fluid resuscitation phase of the hemostatic system, but ignore the local site changes. When PC interacts with its 2 receptor, thrombomodulin and EPCRs, the PC will be activated<sup>[36]</sup>. But the details of the activation still need to be discovered.

## 6. Fibrinogen and hyperfibrinolysis

Fibrinogen is a key substance in maintaining normal hemostasis. Many studies and researches have shown that low fibrinogen is associated with bad outcomes and higher mortality rates in TIC patients and TIC animal models. Patients with TIC who receive fibrinogen supplementation seem to have better outcomes<sup>[37]</sup>.

When hemorrhage occurs, the coagulation system regulates fibrinolysis and maintains the blood clot stable for a while to stop bleeding. High concentrations of thrombin can activate the thrombin-activated fibrinolysis inhibitor (TAFI) and PAI-1, which inhibit the plasmin activation. But if the endothelium is injured, the thrombin will encounter transmembrane glycoprotein thrombomodulin, which activates the PC and furthermore inactivates PAI-1.

One of the major contributors of death in traumatic hemorrhage patients is hyperfibrinolysis<sup>[38,39]</sup>. A study showed that 5% trauma patients develop severe fibrinolysis when they were tested by thromboelastometry and 57% had evidence of moderate fibrinolysis, when plasmin-antiplasmin complex levels rise to more than twice of the normal, and the thromboelastometry test is normal, which means majority of trauma patients have fibrinolytic activation. In the severe injured patients, hyperfibrinolysis occurs early (less than 1 h) and indicates massive transfusion requirements, coagulopathy and hemorrhage shock-related death<sup>[38]</sup>.

In recent reports, the concept of TAFI is raised. When carboxy-terminal lysine residues on fibrin are removed by thrombin and downregulate fibrinolysis, the TAFI will be activated<sup>[40]</sup>. Lustenberger *et al.* recently described the natural history of the circulating TAFI activity and the plasma TAFI antigen levels in traumatic patients<sup>[40]</sup>. They found that on admission, the TAFI activity of patients with TIC is significantly decreased than the patients without TIC and this condition will last for a while (8 days). And there is an inverse correlation between admission TAFI activity and blood transfusion within the first 24 h. We still do not know the mechanism of the phenomenon, so we need more studies on the molecular mechanisms; it will help us to improve our diagnostic sensitivity and make more effective clinical interventions.

## 7. Platelet dysfunction

Although the mechanism of platelet dysfunction is still unclear, there have been some studies that assessed platelet function in trauma patients by thromboelastography-based platelet functional analysis. We found that there are dysfunction of platelet observed in trauma patients, even the platelet count is normal in trauma patients<sup>[41]</sup>. The possible mechanism is used

when patients are critical injured, they will develop TIC, hemorrhagic shock, hypothermia and other status. These status will break the function of the platelet, including activation and adhesion pathway. But there are debates on whether platelet transfusion should be done to the patients whose platelet count is normal, because some studies showed that patient with TIC can receive benefits from platelet transfusion, but others showed that fibrinogen and prothrombin complex concentrate transfusion are enough and there is no need to transfuse platelet<sup>[42]</sup>.

Platelet activation and immediate adhesion, aggregation are very important in resuscitation of trauma patients. So, the function of platelet should be monitored during the treatment and we should pay more attention to how to test its function and maintain it.

## 8. Vicious cycle: hypothermia, acidosis and hemodilution

Hypothermia, coagulopathy, and acidosis are the traditionally lethal triad. In recent years, the hemodilution is added and so called as lethal quartet, which means the uncritical overuse of fluid in hemorrhagic shock resuscitation, then the further dilution of coagulation factors will happen.

Without additional triggers, only 1% in moderate injury patients will develop coagulopathy. The percentage will rise to 39% in severe injury (injury severity score > 25) patients, when combined with hypotension. Similarly, when patients develop acidosis (pH < 7.1), the percentage can rise to 58% and to 98% when injury severity score > 25, together with hypotension (systolic blood pressure < 70 mmHg), hypothermia (temperature < 34 °C) and acidosis (pH < 7.1)<sup>[43]</sup>.

Hypothermia and acidosis both can lead to coagulopathy and they can slow down the speed of the biochemical reactions of the plasma coagulation factor by approximately 5% with 1 °C drop in body temperature. When the individuals temperature is 30 °C, about 75% patients will stop the von Willebrand factor-glycoprotein Ib interaction<sup>[44]</sup>. Hypothermia can inhibit the initiation of thrombin generation and fibrinogen synthesis, but will not affect the fibrinogen degradation. Similarly, when pH is 7.2, the coagulation factor complex activities will reduce to 50% of the normal activity and to 20% at pH 6.8<sup>[7,45]</sup>. The negatively charged phospholipids on the surface of activated platelets help the coagulation factors to action well, but acidosis will interfere the interplay of coagulation factors<sup>[46]</sup>.

Dilution may occur both physiologically and iatrogenically. The reversal of Starling forces and consequent shifts of interstitial fluid into the vascular compartment result in autodilution of coagulation factors. And this condition is aggravated by uncritical fluid infusion. This dilution will cause consumption and inactivation of coagulation factor and coagulation enzymes. Ultimately, the dilutional coagulopathy is proportional to the volume of fluid administered, both *in vitro* and *in vivo*<sup>[47,48]</sup>.

## 9. The importance of rapid diagnostics for TIC

Major traumatic patients are more likely to have hemorrhagic shock, require massive transfusions and have high mortality rate. TIC is the key pathophysiological derangement. When tissue is damaged, the tissue factor will expose and will start the cascade inflammatory response, at last lead to shock and hypoxia. We should imply rapid diagnostics for them and give

proper treatments<sup>[49]</sup>. There are two major tests for TIC diagnosis: standard coagulation tests and thromboelastography (TEG) or thromboelastometry (ROTEM).

Standard coagulation tests include PT, APTT and INR. The advantages of these tests include that these tests play an important role in monitoring the bleeding status, they can help to determine which kind of blood products should be used, they can also reflect the deficiencies of certain coagulation factors and can be used as the markers of TIC, and easy to be provided from most of hospitals<sup>[49]</sup>. The disadvantages include that they are not point-of-care assays, they can not predict the bleeding tendency and they can not reflect the platelet function, thrombin generation and the whole coagulation functions. The turnaround time is long, so the management of TIC will be delayed<sup>[6]</sup>.

TEG and ROTEM measures the clot strength and clot forming time and its advantages include that they can obtain the result rapidly and reflect the whole laboratory clotting condition; they are useful in the management of trauma hemorrhage due to the quick availability of results and they can also strongly predict the need for massive transfusion<sup>[50]</sup>. More and more studies have shown that TEG and ROTEM may be better than traditional coagulation tests in diagnosing TIC because we have found that they are more sensitive than traditional coagulation tests. In recent years, there are a lot of studies using TEG and ROTEM as a rapid identification of TIC. These tests use whole blood clotting function to evaluate the coagulation status and it is shown that trauma patients with TIC (PT<sub>r</sub> > 1.2) have a specific thromboelastogram<sup>[51,52]</sup>. And the clot strength is reduced by 5–10 min, which predicts the need for massive transfusion, bad outcomes and high mortality rate<sup>[53]</sup>. But we still need further large scale studies to prove it and we hope these tests would become good markers of thrombin generation, even become the gold standards in the diagnostics for TIC.

## 10. Conclusions

TIC is the leading cause of death in severely injured patients, which is driven by tissue injury, and will cause systemic hypoperfusion. In the past time, we focused on the fluid resuscitation and maintain patient's vital signs stable, but only a few researches focused on the mechanisms. Recent studies showed that the factors leading to hemostatic abnormalities include hypoperfusion, inflammation response, and sympathoadrenal, which break the endothelial glycocalyx, then the biomarkers of the endothelium will be degraded; the function of the endothelium is damaged, leading to local edema, and furthermore, activating the PC pathway, starting the inflammatory response, meanwhile the platelet function is limited and at last, the hypocoagulability, fibrinolysis, and endothelial hyperpermeability develop, then TIC occurs. Researching the mechanism of TIC can help us to understand the process of it, which helps doctors to recognize the lethal signs earlier and will decrease the preventable mortality of traumatic patients.

## Conflict of interest statement

The authors report no conflict of interest.

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