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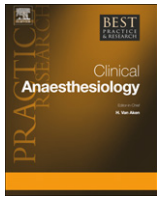

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New insights into acute coagulopathy in trauma patients

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Abnormal coagulation parameters can be found in 25% of trauma patients with major injuries. Furthermore, trauma patients presenting with coagulopathy on admission have worse clinical outcome. Tissue trauma and systemic hypoperfusion appear to be the primary factors responsible for the development of acute traumatic coagulopathy immediately after injury. As a result of overt activation of the protein C pathway, the acute traumatic coagulopathy is characterised by coagulopathy in conjunction with hyperfibrinolysis. This coagulopathy can then be exacerbated by subsequent physiologic and physical derangements such as consumption of coagulation factors, haemodilution, hypothermia, acidemia and inflammation, all factors being associated with ongoing haemorrhage and inadequate resuscitation or transfusion therapies. Knowledge of the different mechanisms involved in the pathogenesis of acute traumatic coagulopathy is essential for successful management of bleeding trauma patients. Therefore, early evidence suggests that treatment directed at aggressive and targeted haemostatic resuscitation can lead to reductions in mortality of severely injured patients.

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Trauma accounts for a significant proportion of death and disabilities worldwide, and it is expected that trauma–related mortality will increase in the near future despite continuing advances in resuscitation, trauma surgery and critical care.[1] Uncontrollable haemorrhage and severe central nervous system injury are known to be the major causes of early death after injury,[2] whereas haemorrhage has been shown to be responsible for a third of all trauma fatalities.[3,4]

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There are two basic mechanisms by which patients may bleed after trauma. First, haemorrhage may occur as a direct result of major injuries (i.e., anatomical bleeding). This bleeding is life–threatening and leads to haemorrhagic shock and exsanguination if not treated readily. Bleeding may be stopped temporarily by external compression and tourniquets; however, surgical or interventional (e.g., arterial embolisation) repair is required for final haemorrhage control. Second, a disturbed coagulation system with diffuse microvascular bleeding may result in a haemorrhage that is no longer localised on the site of injury (i.e., coagulopathic bleeding). This uncontrolled non–surgical haemorrhage may complicate life–saving surgery and force the early termination of operations.[5]

The adverse outcomes of perturbations in blood coagulation are not limited to death from acute blood loss.[6] Organ dysfunction and multiple organ failure are potential consequences of severe injury with subsequent activation of the inflammatory cascade and prolonged shock states.[3] Coagulation is an integral part of the inflammatory system and widespread activation of coagulation results in a systemic inflammatory response syndrome (SIRS) and increased susceptibility to infections and sepsis.[7] This is exacerbated by the adverse immunologic effects of blood transfusions.[8,9] Coagulopathy further worsens outcomes in patients having sustained traumatic brain injury by an increased potential for progression of the intracranial haemorrhage and secondary neuronal loss.[10,11]

Abnormal coagulation parameters can be found in 25% of patients with major trauma and is associated with worse clinical outcome in these patients.[10,12–14] In the past years, there has been a renewed clinical interest to understand the role of the coagulation system in disease and to provide a global functional characterisation of the causes and effects of traumatic coagulopathy. Early evidence suggests that treatment directed at aggressive and targeted haemostatic resuscitation can lead to dramatic reductions in mortality of severely injured patients.[15–18] By specific and goal–directed treatment guided by transfusion algorithms, the coagulopathic trauma patient may be optimised readily, thereby minimising exposure to blood products, reducing costs and improving patient's outcome.[19–21]

Acute traumatic coagulopathy – early phase

Traditionally, the acute traumatic coagulopathy has been thought to be due to lost or inhibited coagulation proteases. Loss may be absolute due to widespread activation and consumption of coagulation factors or relative due to dilution from intravenous fluid therapy. Inhibition can occur due to physical factors such as hypothermia and acidosis.[22] This coagulopathy has also been described previously as systemic acquired coagulopathy (SAC).[23,24]

More recently, it has been recognised that some trauma patients present with an early coagulopathy that is physiologically and mechanistically distinct from the above–mentioned coagulopathy, SAC. Two recent studies have identified an acute traumatic coagulopathy, present on arrival in the emergency department in 25% of patients with major trauma.[10,12] This post–traumatic coagulopathy in the early phase, also called endogenous acute coagulopathy (EAC)[23] or Acute Coagulopathy of Trauma–Shock (ACoTS)[25] is associated with higher transfusion requirements, a greater incidence of multiorgan dysfunction syndrome (MODS), longer intensive care unit (ICU) and hospital stays, and a fourfold increased risk of mortality compared with those with normal coagulation.[10,12]

Tissue injury and systemic hypoperfusion

In examining the mechanism for the coagulopathy in the early phase after trauma, our group recently reported that the combination of traumatic injury and tissue hypoperfusion resulted in a coagulopathy that was associated with a reduction in protein C levels.[14] Protein C is a plasma serine protease and part of the natural anticoagulant pathways.[26] The protein C anticoagulant pathway is initiated when thrombin binds to thrombomodulin (TM) on the surface of the endothelium. An endothelial cell protein C receptor (EPCR) further augments protein C activation by the thrombin–TM complex more than 10–fold *in vivo*. On activation, activated protein C (aPC) exerts its anticoagulant effects by irreversibly inactivating factors Va and VIIIa.[26] In addition, aPC has further anticoagulant activity through its de–activation of plasminogen activator inhibitor 1 (PAI–1) resulting in enhanced fibrinolysis.[27]

Injury severity is closely associated with the degree of coagulopathy.[10,12] However, severely injured patients with normal haemodynamics and no physiologic derangement (i.e., patients not being in shock) rarely present coagulopathic on admission and have a relatively low mortality rate.[14,28] Systemic hypoperfusion (i.e., shock state) itself appears to play a central role in the pathogenesis of early traumatic coagulopathy. There is a dose–dependent association between the degree of tissue hypoperfusion and the level of admission coagulopathy as measured by prothrombin time (PT) and partial thromboplastin time (PTT).[14,28] As the shock progresses, there is an increase in plasma levels of soluble TM and a decrease in protein C levels.[14] In the presence of tissue hypoperfusion, the endothelium seems to express TM which complexes with thrombin to divert it to an anticoagulant function. Less thrombin is available to cleave fibrinogen and thrombin complexed to TM activates protein C, which leads to 'coagulopathy' (by inactivating factor Va and VIIIa) and 'hyperfibrinolysis' (by inhibiting PAI–1). Corroborating this, we found that in the presence of tissue hypoperfusion and increased levels of TM, platelet and fibrinogen levels remained normal, indicating that less thrombin was available to cleave fibrinogen (as it was complexed to TM) and to consume platelets.

While highly suggestive of an activated protein C mediated early traumatic coagulopathy, the above–mentioned human data was observational and correlative, requiring mechanistic confirmation. Therefore, our group developed a translational mouse model of acute traumatic coagulopathy. Using this animal model, our research group demonstrated that the combination of tissue injury and tissue hypoperfusion is required to produce an early traumatic coagulopathy.[23] Furthermore, the data demonstrates that the anticoagulant function of activated protein C is the primary mechanism responsible for the development of the acute traumatic coagulopathy in the early phase after injury. Selective inhibition of the anticoagulant function of protein C in this animal model effectively prevented the development of the acute traumatic coagulopathy in response to injury and hypoperfusion.[23] This result is consistent with our published clinical observations that activation of the protein C pathway correlates with the development of the early, acute traumatic coagulopathy in injured and hypoperfused trauma patients.

Hyperfibrinolysis is common after trauma and is a direct consequence of both tissue injury and shock. As mentioned above, it is mediated by de–inhibition of tissue plasminogen activator (tPA) through the consumption of PAI–1 by activated protein C. Low levels of PAI–1, in combination with the increased release of tPA from the vessel wall will result in hyperfibrinolysis.[29] Contrary to these findings, it has previously been suggested that the de–inhibition of fibrinolysis seen with protein C is not due to this mechanism (reduced PAI–1 activity) but due to a competitive reduction in thrombin activatable fibrinolysis inhibitor (TAFI) activation. TAFI is the main driver of fibrinolysis inhibition, and reduction in TAFI activation (by the competitive binding of protein C to thrombin–TM) has been described as the primary mechanism for de–repression of fibrinolysis with activation of protein C.[30–32] In our previous study, however, we were able to demonstrate an increase in TAFI levels with TM, and a competition between TAFI and protein C, but there was no observable correlation between TAFI and D–dimer levels.[29] Further confirmatory studies are required, but the consumption of PAI–1 by activated protein C appears to be the more clinically important cause of hyperfibrinolysis in trauma patients. Besides the mechanism of inhibiting PAI–1 through activated protein C, endothelial injury results in increased fibrinolysis because of the direct release of tPA.[33] The expression of tPA by the endothelium is also increased in the presence of thrombin.[34] Fibrinolysis is exacerbated because of the combined effects of endothelial tPA release due to ischaemia[35,36] and inhibition of PAI–1 in shock.[14] In addition, in the presence of reduced thrombin concentrations, fibrin monomers polymerise abnormally and are more susceptible to cleavage by plasmin.[37] The purpose of this hyperfibrinolysis is presumably to limit clot propagation to the site of vascular injury. With widespread trauma, however, such localisation may be lost.[25]

Inflammation

The complement system occupies a central role in innate immunity and becomes activated early after trauma in humans.[38,39] Our group has recently reported that there is an amplified activation of complement via the alternative pathway that occurs nearly immediately after injury.[40] Complement activation correlated with injury severity and tissue hypoperfusion and was associated with increased

mortality and with the development of organ failure, such as acute lung injury and acute renal failure.[40] Furthermore, complement has been well studied in ischaemia and reperfusion. Stahl and colleagues have identified the lectin pathway as being the dominant mechanism of complement activation during ischaemia–reperfusion, and have shown that mannose–binding lectin (MBL) binds to a complex of IgM and self–antigens exposed at the surface of endothelial cells during ischaemia.[41] This complex then activates the MBL–dependent portion of the lectin complement pathway. While complement is independently an important mediator of cell injury following tissue hypoperfusion and shock, the link between complement and coagulation is also strong and well described.[42]

Is there an association between the activation of complement and the protein C pathway? Previous studies have reported a direct link between the protein C pathway and complement through TAFI. TAFI is a carboxypeptidase, which, like protein C, is activated by the thrombin–TM complex and which inhibits fibrinolysis by the prevention of plasminogen binding as mentioned above.[31] TAFIa acts directly on complement, cleaving and inactivating C3a and C5a providing a link between thrombin, TM, aPC and the anaphylatoxins of complement.[43] Furthermore, our group has reported evidence of an MBL–initiated activation of the alternative pathway of complement after trauma.[40] In addition, some preliminary unpublished data from our group showed a significant correlation between complement activation, protein C activation and traumatic coagulopathy in humans. Furthermore, TM expression and protein C activation after ischaemia–reperfusion seems to be complement–dependent, indicating a link between complement activation and the early phase of acute traumatic coagulopathy caused by haemorrhage and severe trauma (Fig. 1).

Traumatic coagulopathy – later phase

In the later phase after trauma, acute traumatic coagulopathy mediated through tissue injury and shock may be worsened by the classically known causes of traumatic coagulopathy, that is,

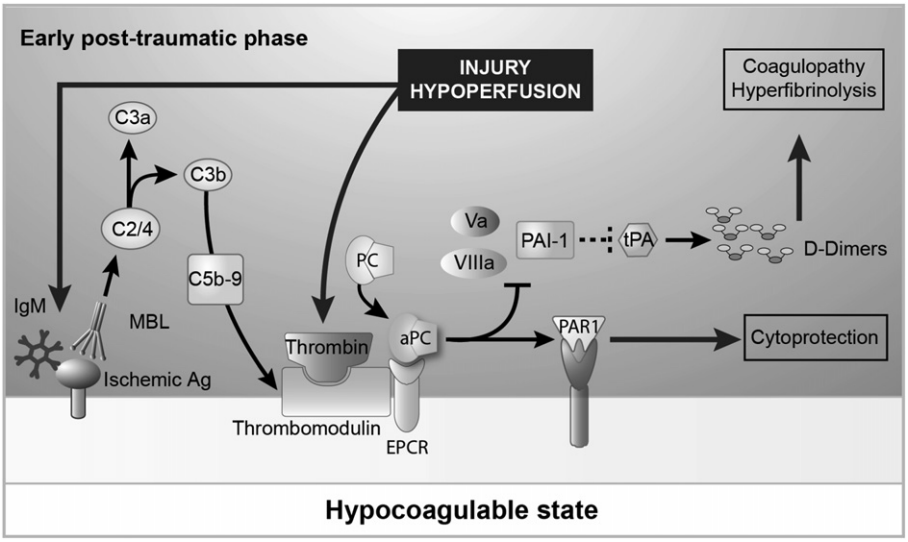

Fig. 1. Early post–traumatic phase. Tissue trauma and shock with systemic hypoperfusion appear to be the primary factors responsible for the development of acute traumatic coagulopathy in the immediate post–injury phase. As a result of overt activation of protein C pathway, the acute traumatic coagulopathy is characterised by *coagulopathy* (de–activation of the coagulation factors Va and VIIIa) in conjunction with *hyperfibrinolysis* (de–repression of fibrinolysis). In addition to its anticoagulant effects, activated protein C proteolytically activates the cell surface receptor, protease–activated receptor–1 (PAR–1), to produce several *cytoprotective* effects including anti–inflammatory properties, anti–apoptotic activity and protection of endothelial barrier function, all being required for acute survival during shock. The complement cascade is being activated immediately after trauma via the lectin pathway (mannose binding lectin, MBL), amplified via the alternative pathway and seems to be implicated in the activation of the protein C pathway early after severe trauma.

consumption, dilution, acidosis and hypothermia. The inflammatory cascade thereby plays a further role, central but complex, as there is a significant cross–talk between the coagulation and the inflammatory systems.[44]

Activation and consumption

Tissue injury leads to vascular damage with expression of subendothelial structures into the circulatory system, thereby expressing tissue factor and initiating the clotting cascade. The severity of injury has been shown to directly correlate with the amount of thrombin generated and activation of the coagulation cascade results in consumption of coagulation factors.[14] However, there is little evidence to support consumption of clotting factors as a relevant mechanism for the early phase of the acute traumatic coagulopathy: in patients without systemic hypoperfusion, coagulation parameters such as PT and PTT were typically not prolonged, regardless of the amount of thrombin formed.[14] Furthermore, platelets and fibrinogen levels were within normal ranges in patients with acute traumatic coagulopathy.[14,29]

Specific injury patterns such as severe traumatic brain injury or long–bone fractures are frequently associated with the development of a coagulopathy.[45–47] In patients with traumatic brain injury, it has been postulated that brain–specific thromboplastins are released into the circulation, with subsequent inappropriate consumption of coagulation factors causing a disseminated intravascular coagulation (DIC)–like coagulopathy.[48] There is, however, no evidence to support this DIC hypothesis in the early phase after trauma. More recent data suggest that hyperfibrinolysis due to tissue damage and hypoperfusion with consecutive activation of the protein C pathway may be the predominant mechanism of coagulopathy in these patients.[49–51] The same holds true for multiple long–bone fractures with marrow fat embolisation. Here, it appears that the resulting coagulopathy is also caused by tissue injury, shock and inflammation, rather than through a bone marrow–specific pathogenesis.[52] The use of DIC to describe traumatic coagulopathy is, therefore, misleading and should be avoided.

Dilution

Dilutional coagulopathy is one of the most common causes of bleeding after massive transfusion in the later phase after trauma.[15,53] Haemorrhagic shock leads to a net flux of extracellular water into the vascular space because of a lowered intravascular hydrostatic pressure due to bleeding. This dilution of coagulation proteins is further enhanced by external fluid resuscitation. In addition to the dilutional effect, which may be calculated mathematically, side effects on coagulation from different fluids (e.g., crystalloids and colloids) with different compositions (e.g., unbalanced vs. balanced solutions and normotonic vs. hypertonic solutions) have to be considered.[54–56]

It is still unclear which type of fluid should be employed in the initial treatment of the bleeding trauma patient.[19] Although several meta–analyses have shown an increased risk of death in patients treated with colloids than in patients treated with crystalloids[57–61] and three of these studies showed that the effect was particularly significant in a trauma subgroup,[57,59,60] a more recent meta–analysis showed no difference in mortality between colloids and crystalloids.[62] The SAFE (Saline vs. Albumin Fluid Evaluation) study compared 4% albumin with 0.9% sodium chloride in a large number of ICU patients and showed that albumin administration was not associated with worse outcomes; however, there was a trend towards higher mortality in the trauma subgroup that received albumin.[63]

Several studies have shown that infusion of colloid plasma expanders induces coagulopathy to a greater extent than simple dilution, thereby increasing the risk of bleeding.[53,54,64] Several mechanisms have been proposed: some studies have shown that colloids may reduce levels of von Willebrand factor (vWF) and factor VIII,[65,66] whereas other studies have reported on masked expression of glycoprotein IIb/IIIa on activated platelets.[67,68] More recently, an acquired deficiency of fibrinogen with abnormal fibrin polymerisation have been proposed as the main determinant of dilutional coagulopathy.[69,70] The dilutional coagulopathy observed after administration of moderate amounts of hydroxyethyl starch solutions could be completely corrected by administration of fibrinogen concentrate. In addition, bleeding and postoperative transfusion requirements were significantly reduced after reversing this dilutional coagulopathy by fibrinogen concentrate.[69,70] Fibrinogen is the final substrate in

the clotting cascade and has been described as the earliest coagulation factor to reach a critically low threshold level in bleeding patients.[71] Furthermore, fibrinogen has been suggested as a key coagulation factor needed to ensure sufficient and stable haemostasis during severe haemorrhage.[72–74]

Transfusion of packed red blood cells (pRBCs) also results in dilution of clotting factors and reduction in clotting ability.[15,22,75] These cells (pRBCs) contain no functional platelets and only a little plasma. By the time 10–12 units of pRBCs have been administered, at least two–thirds of the patient's original plasma has been lost. At that time, a prolongation of PT and PTT will be measurable by more than 1.5 times mid–range of normal.[76,77] Platelets are lost more slowly than plasma proteins because a third of platelets are sequestered in the spleen and an additional fraction are adherent to the endothelium. As a result, platelet counts rarely fall below 100 000 per mm^3 before 10–20 units of pRBCs have been administered in situations of otherwise uncomplicated haemorrhage. In a study of 39 massively transfused patients, platelet counts below 50 000 per mm^3 were found in three of four patients who received 20 or more units of RBC products and in no patients who received less than 20 units.[77] As a rule of thumb recognised for a long time, these data suggest that coagulation factor replacement is mandatory at the latest in patients who receive 12 or more units of pRBCs, and platelet replacement is necessary in patients who receive 20 or more units of pRBCs.[77,78]

Acidosis

The association between high lactate levels and increasing risk of death was first described over 40 years ago.[79] Since then, several investigators have demonstrated increasing risk of death with metabolic acidosis as demonstrated by arterial pH, lactate and base deficit clearance.[80] The deleterious effects of acidosis on the cardiovascular system include decreased cardiac contractility and cardiac output, vasodilation and hypotension, decreased hepatic and renal blood flow, bradycardia and increased susceptibility to ventricular dysrhythmias.[81] Acidosis directly reduces the activity of the extrinsic and intrinsic coagulation pathways as measured by PT and PTT and also diminishes platelet function as measured by platelet aggregation. These adverse effects are generally not seen until pH decreases below 7.2.[82] Therapy for metabolic acidosis remains directed toward correcting the underlying tissue hypoperfusion. Resuscitation endpoints include normalisation of arterial pH, base deficit and lactate. Interestingly, simple correction of the acidosis by buffer therapy does not seem to correct the negative effects of acidemia on coagulation.[83,84] Clinical trials have failed to demonstrate any clear advantage of bicarbonate administration, whereas the potential adverse effects are well documented.[85]

If transfusions with pRBCs are required, the following storage effects on acid–base homeostasis have to be considered: after 2 weeks of storage, pRBCs have a pH below 7.0, and each unit has an acid load of approximately 6 mEq.[86] One of these mEq of acid comes from the fact that pRBCs are made from venous blood with a starting pH of 7.35, a second mEq is acquired in buffering the citric acid in the anticoagulant and 4 mEqs are generated by glycolysis during pRBC storage. Seven units of pRBCs are expected to increase the whole body base deficit of a 70–kg man by 1 mEq l.

Hypothermia

Hypothermia is a frequent consequence of severe injury and subsequent resuscitation. It is estimated that as many as 66% of trauma patients arrive in the emergency department with hypothermia.[87] Gregory and colleagues found that hypothermia developed at some point in 57% of the trauma patients studied, and that temperature loss was most severe in the emergency department setting.[88] There is, however, very little effect of hypothermia on coagulation protease function and clinical bleeding at temperatures above 33 °C.[82,89,90] On the other side, body temperatures less than 33 °C produce a clinically significant coagulopathy that is functionally equivalent to factor deficiency states seen when coagulation factor concentrations are less than 50%.[91] Thrombin generation on platelets is reduced by 25% at 33 °C. The average size of aggregates formed by thrombin–activated platelets was decreased by 40% at 33 °C and platelet adhesion was reduced by 33%.[92] Adverse clinical effects such as cardiac dysrhythmias, reduction in cardiac output, increase in systemic vascular resistance and a left shift in the oxygen–haemoglobin saturation curve have been described. Mortality rates as high as 100% are seen in patients with severe hypothermia and severe injury. The most

significant effect of hypothermia in trauma is coagulopathic bleeding due to prolonged clotting cascade enzyme reactions, dysfunctional platelets and fibrinolysis.[91,92]

Resuscitation with cold blood and fluids creates a vicious cycle of worsening haemodilution, acidosis, hypothermia and coagulopathy. Interestingly, five units of cold pRBCs would be expected to reduce the body temperature of a 70–kg man by about 1 °C.[86]

Inflammatory response to injury

In the later course after injury, the inflammatory response shifts the haemostatic mechanisms in favour of thrombosis (Fig. 2). Multiple mechanisms are at play, including up–regulation of tissue factor leading to the initiation of clotting, amplification of the clotting process by augmenting exposure of cellular coagulant phospholipids, inhibition of fibrinolysis by elevating PAI–1 and decreases in natural anticoagulant pathways, particularly targeted towards down–regulation of the protein C anticoagulant pathway through multiple mechanisms.[7,44] Part of the explanation for this may lie in the early activation of protein C resulting in its depletion. As protein C is synthesised in the liver, it will take several days for protein C levels to return to normal, during which time a hyper–coagulable state will exist that is known to predispose to venous thrombosis.[93] Patients who present with coagulopathy on admission should therefore be considered at increased risk of deep venous thrombosis and pulmonary embolism and receive prophylaxis accordingly.

Activated protein C also acts via the cell surface receptor, protease–activated receptor–1 (PAR–1) to produce several cytoprotective effects.[94] These effects include anti–inflammatory properties, anti–apoptotic activity and protection of endothelial barrier function.[95–97] Tumour necrosis factor (TNF) α and other inflammatory mediators can down–regulate EPCR and TM and interleukin (IL)–6 can depress levels of protein S in experimental animals. A depleted or inhibited protein C pathway function increases cytokine elaboration, endothelial cell injury and leucocyte extravasation in response to endotoxin, processes that are decreased by infusion of aPC.[7,44] Since thrombin can elicit many inflammatory responses in microvascular endothelium, loss of control of microvascular thrombin

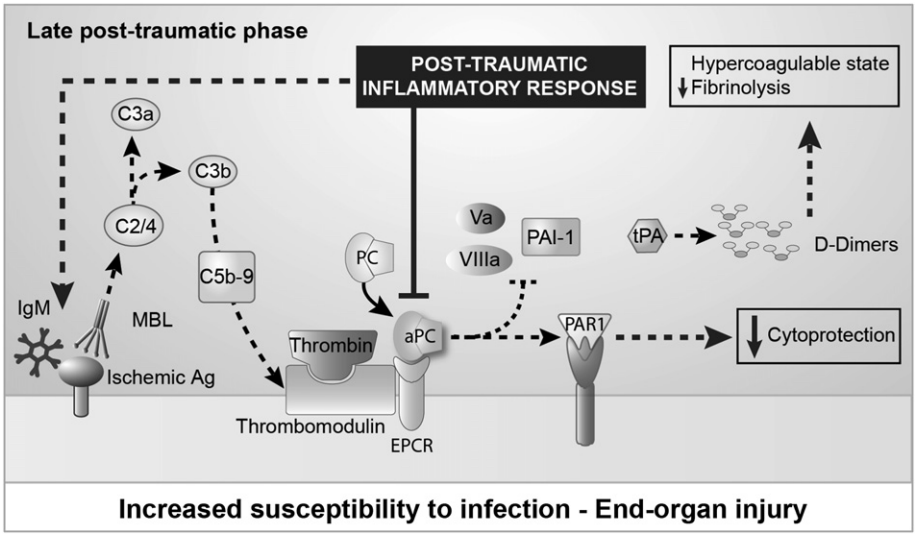

Fig. 2. Late post–traumatic phase. In the later phase after trauma, there is the development of a pro–coagulant activity associated with low plasma levels of activated protein C (aPC), an inhibition of the fibrinolysis caused by elevated plasma levels of plasminogen activator inhibitor 1 (PAI–1) and a downregulation of complement activation due to low plasma levels of mannose–binding lectins (MBL) and significant impairment of C3b deposition via the lectin and alternative pathways. These coagulation and complement abnormalities increase the susceptibility to hypercoagulability with late thrombosis, infection and end–organ injury. At the later time points the dashed lines represent inhibited or depleted pathways.

generation due to impaired protein C pathway function probably contributes to microvascular dysfunction, infections and end–organ injury in the later phase after trauma (Fig. 2).

Conclusions

Tissue trauma and shock with systemic hypoperfusion appear to be the primary factors responsible for the development of acute traumatic coagulopathy in the immediate post–injury phase. As a result of overt activation of the protein C pathway, acute traumatic coagulopathy is characterised by coagulopathy in conjunction with hyperfibrinolysis.[21] This coagulopathy can then be exacerbated by subsequent physical and physiologic derangements associated with ongoing haemorrhage and inadequate resuscitation or transfusion therapies.

Knowledge of the different mechanisms involved in the pathogenesis of acute traumatic coagulopathy has clear significance for the successful management of bleeding trauma patients. In the early phase after trauma, efforts at augmenting the clotting factor pathway through pre–emptive blood transfusions and factor concentrates may prove ineffective until shock and associated hypoperfusion are corrected. Underlining our hypothesis, other research groups recently suggested a revised bloody vicious cycle (hypothermia, acidosis and coagulopathy)[98] with an 'fresh–frozen plasma (FFP)–resistant' pathway (endogenous acute coagulopathy (EAC)) as opposed to a later 'FFP–sensitive' route leading to progressive SAC with associated clotting factor deficiency.[99,100] To provide optimal care to haemorrhaging trauma patients and to prevent further bleeding, the leading pathomechanism of coagulopathy needs to be diagnosed and treated readily. Aggressive and goal–directed haemostatic resuscitation can thereby minimise exposure to blood products, reduce costs and improve patient's outcome.[15–17,19–21]

Practice points

* Of the trauma patients, 25% present with a clinically significant coagulopathy in the emergency department on arrival.
* Trauma patients with coagulopathy on admission to the emergency department are four times more likely to die.
* The acute coagulopathy of trauma in the early phase is due to shock with systemic hypoperfusion and consecutive activation of the TM–protein C pathway (EAC).
* Knowledge of the different mechanisms involved in the pathogenesis of acute traumatic coagulopathy has clear significance for the successful management of bleeding trauma patients.

Research agenda

* The exact molecular mechanisms by which the TM–protein C pathway is activated needs to be further elaborated in trauma patients.
* What happens to the other natural anticoagulant pathways after trauma?
* The complex interaction between inflammation and coagulation in trauma patients needs further in–depth studies.
* What are the mechanisms of an exhausted TM–protein C pathway after trauma on patient outcome?

Conflict of interest

In the past 5 years, Dr Ganter has received honoraria or travel support for consulting or lecturing from the following companies: CSL Behring GmbH, Hattersheim am Main, Germany; GlaxoSmithKline GmbH & Co. KG, Hamburg, Germany; Essex Pharma GmbH, Munich, Germany.

Dr Pittet has no conflict of interests to declare related to this article.

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