Pathogenesis of acute traumatic coagulopathy

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Acute traumatic coagulopathy (ATC) is an early endogenous process, driven by the combination of tissue injury and shock that is associated with increased mortality and worse outcomes in the polytrauma patient. This review summarizes our current understanding of the pathophysiology of ATC and the role of rapid diagnostics in the management of severe trauma hemorrhage. In particular we consider diagnostic and therapeutic strategies for bleeding trauma patients with short versus long prehospital times and the concept of remote damage control resuscitation. Endothelial activation of Protein C is a central mechanism of ATC, which produces rapid anticoagulation and fibrinolysis following severe trauma. Continued blood loss, hypothermia, acidosis, and hemodilution potentiate ATC and lead to a global derangement in all components of hemostasis. The contribution and interplay between platelet activity, fibrinogen utilization, endothelial dysfunction, and neurohormonal pathways remain to be defined in ATC pathogenesis but may offer novel therapeutic targets. Conventional laboratory-based tests of coagulation have a limited role in the early management of major trauma hemorrhage. TEG and ROTEM provide a rapid evaluation of clot dynamics in whole blood and are of greater value than coagulation screens in diagnosing and managing trauma hemorrhage.

INTRODUCTION

Trauma-induced coagulopathy (TIC) is a multifactorial, global failure of the coagulation system to sustain adequate hemostasis after major trauma. Derangements in coagulation screens are detectable in the hyperacute phase following severe trauma thus supporting the hypothesis of an early endogenous process.[1] This acute traumatic coagulopathy (ATC) is driven by the combination of tissue trauma and systemic hypoperfusion and characterized by global anticoagulation and hyperfibrinolysis.[2] Coagulation is an integral part component of the innate immune system, and endothelial activation of Protein C (PC) appears to be a central mechanism of ATC,[3-5] possibly as part of the posttraumatic inflammatory response. Further blood loss, hemodilution by intravenous crystalloids or hypocoagulable blood products, e.g., red blood cells (RBCs), acidemia, consumption of clotting factors, and hypothermia occur over time and exacerbate the already deranged coagulation response to give rise to TIC.[6]

Patients presenting with ATC have a mortality approaching 50%, a greater need for transfusion of blood products and significantly higher morbidity.[1] Targeted transfusion strategies may allow significant improvement in outcomes; however, optimal therapeutic interventions are restricted by our limited understanding of the pathogenesis of ATC. This review briefly summarizes the current thinking on the dominant mechanisms of ATC and the role of rapid diagnostics for early identification of this coagulopathy. Further we discuss potential strategies, both diagnostic and therapeutic, for patients with short versus long prehospital scene and transport, and the concept of remote damage control resuscitation.

CHARACTERIZING ATC AS A CLINICAL SYNDROME

ATC is defined by a functional reduction in clot strength with smaller changes in clotting times.[7] With a threshold of clot amplitude at 5 minutes of <35 mm, ROTEM can identify ATC at 5 minutes and predict the need for massive transfusion with comparable results demonstrated using rapid TEG.[8] It develops rapidly, and studies have shown up to 25% of severely injured patients have an abnormal coagulation status on arrival at hospital.[6] Exsanguination accounts for 40% of early trauma mortality, and presentation with an established coagulopathy is associated with a fourfold increase in mortality and significantly more morbidity in the survivors. In an epidemiological study of over 5000 patients, a prothrombin ratio (PTr) of 1.2 was found

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to be a clinically significant threshold for the definition of ATC.[9] PTr > 1.2 was associated with a stepwise increase in mortality and blood product requirements, and the authors were able to demonstrate that the often cited threshold for coagulopathy of PTr/INR > 1.5 fails to detect 16% of patients with worse outcomes.

Large observational studies have shown that ATC, defined by prolongations of clotting times, is an independent predictor of multiorgan failure, septic complications, and critical care stay.[10] Clinical and experimental studies have shown that the incidence of ATC is closely correlated with the severity of tissue trauma and most commonly evident in the presence of tissue hypoperfusion (metabolic acidosis).[9] In both animal models and human observation ATC occurs prior to any dilutional effects of large volume crystalloid resuscitation. Furthermore patients develop coagulopathy in the absence of hypothermia, significant enough (<33°C) to impair fibrinogen synthesis, thrombin generation, or platelet function, suggesting an alternative mechanism was responsible for ATC.[6]

In the context of the prehospital phase of trauma care, ATC may be the dominant mechanism in the early minutes to hours, but other recognized causes of coagulopathy are likely to play a contributory role as the global entity of TIC develops. Protracted scene times (>2 hr) due to entrapment or extended transfer times in the military and austere environment may alter the clinical syndrome. Prolonged shock, hypothermia, and volume depletion may potentiate ATC or function as independent mechanisms of coagulopathy. Diagnostic modalities and targeted resuscitation in the prehospital phase must take all of these factors into consideration. Based on the potential for alternative underlying pathophysiology, patients in the field in need of remote damage control resuscitation (RDCR) may require a modified transfusion strategy compared with the patient who has a scene time <30 minutes and immediate access to the full gambit of trauma care.

MECHANISMS OF ATC

The cell-based model of hemostasis recognizes the fundamental importance of the phospholipid membrane of the thrombocyte, and the endothelium, as a platform for the balanced assembly and lysis of coagulation factors to produce a stable clot localized to the site of injury. There is little evidence to suggest that tissue trauma in isolation consumes clotting factors akin to disseminated intravascular coagulation (DIC).[11] Tissue damage initiates coagulation following exposure of procoagulant substances, e.g., tissue factor in the endothelium, but coagulopathy is rare in severely injured patients without shock. Profound acidosis (pH < 7.1) appears necessary for coagulation dysfunction with only moderate prolongations of clotting times. The precise effects of acidemia on coagulation in vivo remain unknown as clinically it is difficult to ascertain the precise inhibitory effects of pH versus tissue hypoperfusion and shock.

Current transfusion strategies utilize high dose fresh frozen plasma (FFP) on the premise that thrombin generation is impaired in the coagulopathic trauma patient. However, coagulation factors apart from factor V are well maintained in the immediate phase after injury[3,12] at levels far higher than that experimentally shown to prolong clotting tests, e.g., <30% activity. Furthermore two clinical studies have reported that thrombin generation may actually be increased after injury suggesting other components of hemostasis may be of greater mechanistic importance in ATC.[13] Numerous retrospective studies have suggested improved outcomes with early high dose plasma although the optimal ratio of blood to plasma has not been defined. Hypothetically, the efficacy of early FFP may not simply be derived from replacement of clotting factors. Preliminary data have highlighted the repair and restoration of the endothelial glycocalyx as a possible alternative source of benefit.[14]

ENDOGENOUS ANTICOAGULATION AND THE PC PATHWAY

We have previously proposed that ATC is functionally mediated by activation of PC.[15] In both human and experimental models, shock with tissue injury is associated with early depletion of PC, increased plasma thrombomodulin, and low levels of factor V, suggesting activation of the PC pathway in ATC.[3,16] More recently, Johansson and colleagues have examined the neurohormonal-enthothelial axis and demonstrated an association between degradation of the glycolcalyx and shock/tissue hypoperfusion.[17] Importantly, thrombin generation, activation of PC, and hyperfibrinolysis can all be triggered by endothelial glycocalyx degradation. Hypothetically, tissue hypoperfusion may initiate a "thrombin switch" that diverts thrombin from fibrin generation to the production of activated PC (aPC) and early systemic anticoagulation. In the presence of tissue hypoperfusion and significant thrombin generation following tissue trauma, the endothelium expresses thrombomodulin, which complexes with thrombin to divert it to an anticoagulant function. Less thrombin is available to cleave fibrinogen and thrombin complexed to thrombomodulin activates PC, which inhibits cofactors Va and VIIIa.

Consistent with earlier smaller studies[5] we have recently provided further evidence to support the PC hypothesis by measuring aPC in a cohort of 300 trauma patients.[4] High levels of aPC were associated with reduced clot strength, limited changes in clotting times, increased mortality, and greater transfusion requirements. Compared with factor V and VIII, proteases that do not undergo aPC-mediated cleavage (factors II, VII, IX, and X) were

maintained at normal levels of activity. Corroborating the potential importance of the PC pathway, in mice subjected to trauma hemorrhage, monoclonal antibody blockade of aPC anticoagulant function or genetic suppression of the PC pathway attenuates ATC.[16] This process may, in part, explain a potential mechanism for the limited effects to procoagulant therapy (e.g., high dose plasma, activated factor VIIa) exhibited by some severely injured patients if it results in further increases of aPC levels and paradoxical anticoagulation.[10] FFP may, however, have additional effects over and above replacement of clotting factors, with restorative effects on the glycolcalyx, which in experimental models has been shown to be associated with improved outcomes.[14] However, in combination these findings suggest activation of PC is a key mechanism of ATC and provide new translational scope for the management of trauma hemorrhage.

FIBRINOGEN AND FIBRINOLYSIS

Normal hemostasis is dependent on fibrinogen as a substrate for clot formation, but there is controversy over the critical level for adequate hemostasis.[10] Fibrinogen levels have been shown to fall rapidly in both experimental models of ATC and in numerous retrospective clinical studies, although not to levels that would have historically triggered fibrinogen replacement (<0.8-1.0 g/L). Fibrinogen depletion is well documented in massive transfusion and associated with poor outcomes. Further, fibrinogen levels fail to normalize during damage control resuscitation despite the provision of high ratios of plasma and platelets.[18] Fibrinogen supplementation is able to correct coagulopathy as demonstrated by viscoelastic tests of coagulation (ROTEM, TEG).[10] Patients who receive additional fibrinogen supplementation appear to have better outcomes suggesting an important role for fibrinogen in the pathophysiology and management of ATC.

The precise mechanism by which fibrinogen is lost remains to be elucidated since factor V is the only factor to reach critical levels (<30%), and pathologic findings suggest DIC is exceptionally uncommon in trauma.[11] Profound acidosis, severe hypothermia (<32°C), and hemodilution have been shown to lower fibrinogen although in the early postinjury ATC phase of TIC these factors are not significant. Studies in severely head-injured patients have demonstrated an association between excessive fibrinogen breakdown, increased clot size, and poor outcomes.[19] Activation of coagulation releases the inhibitory break on multiple lytic pathways, and fibrinogenolysis is one possible explanation for the reduction of fibrinogen associated with ATC.

Hyperfibrinolysis is a key component of ATC and present in the majority of severely injured patients.[20] Detection is limited by the relatively insensitive diagnostic tools available, e.g., ROTEM, TEG, although laboratory markers of fibrinolysis are grossly elevated in the immediate phase after injury. Shock, hypoxia, circulating catecholamines, and endothelial damage are potent activators of fibrinolysis, but the precise mechanism by which it is activated remains unclear. Trauma patients with shock have been shown to have a reduction in plasminogen activator inhibitor-1 (PAI-1) and elevated tissue plasminogen activity.[2] Activated PC in excess will consume PAI-1 and results in a "de-repression" of fibrinolytic activity thus further implicating the PC pathway in the pathogenesis of ATC.

Antifibrinolytic agents such as tranexamic acid (TXA) have been comprehensively shown to reduce blood loss in elective surgery and more recently improve survival in trauma hemorrhage following the results of the large multicenter CRASH-2 trial.[21] Subgroup analysis demonstrated that TXA was most effective in patients with shock (systolic blood pressure <75 mmHg) as may be expected since this cohort of patients is likely to have maximal activation of fibrinolysis. The precise mechanism of action in trauma hemorrhage is unclear—intuitively early administration of TXA would inhibit fibrinolysis in the early stages, augment clot formation, and reduce blood requirements. TXA activates anti-inflammatory pathways[22] and theoretically could modulate the immune response in major trauma hemorrhage, theoretically reducing the harmful effects of the inflammatory sequela.

PLATELET DYSFUNCTION

Platelet activation and fibrin generation are mutually dependent processes—completion of platelet prothrombinase (FXa/Va) assembly on the phospholipid membrane generates a thrombin burst of sufficient magnitude to polymerize and clot fibrinogen. Platelet dysfunction in ATC is largely unknown but is apparent in the severely injured patient.[23] ATC and the combined effects of shock, hypothermia, etc. would theoretically produce aberrant platelet function through disruption of activation and adhesion pathways but to date only very limited mechanistic study has been performed in trauma patients.

Massive transfusions of RBCs and FFP and other intravenous fluids will give rise to dilutional thrombocytopenia. However, in the early stages of trauma hemorrhage, numerous studies have shown thrombocytes are maintained at levels not expected to contribute to a clinically significant coagulopathy.[13] Platelet transfusion may not be essential for correction of ATC or TIC as fibrinogen replacement will reverse the reductions in clot strength evident in thrombocytopenia. In addition in a goal-directed trial utilizing ROTEM and transfusion algorithms for the management of ATC approximately 1/3 of patients received only fibrinogen and prothrombin complex

concentrate with no need for platelet transfusion.[24] However, transfusion of normally functioning platelets may be associated with additional benefits such as restoration of the endothelium and modulation of infective and inflammatory sequela.

Severe injury results in increased platelet activation and faster rates of adhesion and aggregation. Functional platelet defects as measured by whole blood aggregometry appear minor but in parallel with platelet count there are significant differences between survivors and nonsurvivors. The most challenging question remains how to study those thrombocytes actively involved in clot formation at the site of injury. It therefore remains to be seen if those free, circulating platelets sampled and analyzed are reflective of "active" platelet function.

RAPID DIAGNOSTICS FOR EARLY IDENTIFICATION OF ATC

Laboratory clotting screens are of limited value in the management of trauma hemorrhage due to delayed availability of results, poor predictive power for massive transfusion, inability to quantify clot propagation versus clot lysis or overall clot strength.[10] We have previously defined ATC primarily as a reduction in clot strength as measured at 5 minutes by ROTEM (CA5 $\leq$ 35 mm) with only minor changes in PT and partial thromboplastin time.[7] These coagulation tests are measured in platelet poor plasma, and in the context of the cell-based model of hemostasis it is questionable what the values actually mean. Prolongations are associated with increased mortality and transfusion requirements, and it is conceivable that they are simply a marker of injury severity, metabolic dysfunction, or inflammation associated with tissue trauma.

In the last 10 years there has been a rapid expansion in the use of ROTEM and TEG for the rapid identification of ATC. Both viscoelastic tests of coagulation utilize whole blood to evaluate clot dynamics, and we have shown that trauma patients with ATC (defined as PTr > 1.2) have a "signature" thromboelastogram.[7] The reduction in clot strength is identifiable within 5-10 minutes and can be used to predict need for massive transfusion with reasonable accuracy—detection rate of 71% versus 43% for PTr > 1.2. Some small studies have already suggested ROTEM can be used for goal-directed therapy, but endpoints have yet to be validated, and larger studies are required to identify whether ROTEM and TEG triggers are associated with improved outcomes. A major benefit of these whole blood assays is their ability to detect hyperfibrinolysis albeit with limited sensitivity as lytic traces are only apparent in the most extreme cases.[10] Global tests of coagulation are good markers of thrombin generation and may become the new gold standards in hemostasis particularly in the acute setting of a multifactorial coagulopathy such as TIC.

SUMMARY

ATC is an early endogenous process driven by tissue injury with systemic hypoperfusion. Activation of PC with subsequent anticoagulation, hyperfibrinolysis, and fibrinogen depletion is a dominant mechanism of ATC. Other recognized causes of coagulopathy in trauma such as hypothermia, acidosis, and exogenous hemodilution exacerbate the hypocoagulable state and constitute a global TIC. Fibrinogen metabolism in trauma, platelet dysfunction, and the role of the endothelial glycocalyx remain to be fully elucidated but remain likely candidates in the multifactorial pathogenesis of ATC. Further delineating the temporal relationship of ATC and TIC, in addition to understanding what are the dominant mechanisms of coagulopathy in the prolonged prehospital phase, may alter RDCR strategies. Devices such as ROTEM and TEG improve the speed of diagnosis, but further work to fully determine the pathophysiology of ATC is essential for translational research if we are to optimize the early treatment of trauma hemorrhage.

CONFLICT OF INTEREST

None.

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