Acute traumatic coagulopathy

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Purpose of review
Recent therapeutic and observational studies have demonstrated improved survival with better management of haemostasis early after injury. This review delineates our current understanding of the clinical importance, aetiology and pathophysiology of acute traumatic coagulopathy (ATC).

Recent findings
Trauma causes an acute disruption of the equilibrium between all components of haemostasis (coagulation, anticoagulation, fibrinolysis, platelets and endothelium). In patients with a combination of severe tissue damage and systemic hypoperfusion, this will progress rapidly to an endogenous coagulopathy that is independently associated with worse outcomes. New discoveries of the interactions between neurohormonal, vascular, and coagulation systems are beginning to explain how this haemostatic impairment develops and offer novel targets for therapeutic manipulation. Routine coagulation screening tests are ineffective for diagnosing ATC and guiding resuscitation in real-time. Viscoelastic coagulation tests (such as ROTEM or TEG) have emerged as practical, rapid and sensitive diagnostic modalities. Their role in therapeutic targeting requires further validation.

Summary
Conventional concepts of traumatic coagulopathy as a late occurring condition in response to iatrogenic haemodilution are redundant. ATC is an endogenous impairment of haemostasis that begins at the moment of injury. Further outcome improvements are possible with better understanding of the process by which this coagulopathy develops and how it may be inhibited.

Keywords
coagulopathy, fibrinolysis, thromboelastometry, transfusion, trauma

INTRODUCTION
Recognition of an acute component to the coagulopathy of trauma has revolutionized our comprehension and clinical management of haemostasis after injury. We now know that disruption of haemostatic equilibrium begins at the moment of traumatic impact [1**]. Innate physiological responses are initiated by tissue injury and blood loss producing this endogenous acute traumatic coagulopathy (ATC) [2,3**]. Subsequent medical interventions exacerbate this through multiple mechanisms that together contribute to the multifactorial trauma-induced coagulopathy (TIC). Fortunately, new insights into these mechanisms have led to clinical studies demonstrating a significant potential for improved outcome [4,5**]. More lives can be saved by the continued refinement of our haemorrhage control strategies. This review aims to summarize recent advances in our understanding of ATC, from both experimental and clinical perspectives.

ACUTE TRAUMATIC COAGULOPATHY: AN ENDOGENOUS PRECURSOR OF TRAUMA-INDUCED COAGULOPATHY
ATC develops rapidly and has been identified within minutes of injury. Floccard et al. [1**] analysed blood samples taken from 45 trauma patients at the accident scene and found that 56% already had an abnormal coagulation status only 25 min after injury. Similarly, Carrol et al. [6] documented a variety of abnormal TEG measurements in the blood of 161 trauma patients taken prehospital. Thus, ATC is established by the time patients
arrive in the emergency department and exacerbates uncontrolled bleeding.

Both severe tissue trauma and systemic hypoperfusion appear to be prerequisites for the development of ATC. In a retrospective study of over 5000 patients brought to five international trauma centres, we identified that neither variable alone, regardless of the severity, was associated with clinical coagulopathy [3**]. Clinically relevant prolongations in prothrombin times (PTs) were only seen with combined increases of injury severity score (ISS) and base deficit. The worst coagulopathies were seen in those with ISS more than 35 and base deficit less than –12 mEq/l. Simmons et al. [7*] retrospectively divided 450 combat casualties requiring massive transfusion into cohorts injured by either explosion (high-tissue injury) or gunshot wound (GSW, low-tissue injury). Patients were similar with regard to age, ISS, SBP, temperature, Glasgow Coma Score (GCS), haemoglobin and mortality. The patients injured by explosion presented more tachycardic, with worse base deficit, and a higher International Normalized Ratio (INR) compared with the patients injured by GSW. In addition, the incidence of coagulopathy (INR > 1.5) was greater in the explosion cohort. When comparing only those patients who arrived with a base deficit less than –6 mEq/l, patients injured by explosion still had a higher INR than those injured by GSW. Although shock seems to be the main driver for ATC, the presence of some tissue damage is necessary in its pathogenesis.

Other mediators of TIC (hypothermia, acidosis, haemodilution) develop over time from injury as a consequence of haemorrhage, hypoperfusion, exposure and resuscitation with hypocoagulable resuscitation products. However, hypothermia and acidosis probably do not produce a clinically relevant effect until body temperatures are under 33°C and/or pH is below 7.2 [8]. High volumes (>3 l) of crystalloid or colloid fluid administered prehospital are independently associated with a worse emergency department coagulation profile [9*]. Hüßmann et al. [10] performed matched pair analysis on two groups of 1351 trauma patients that had been divided into low volume prehospital resuscitation (<1500 ml crystalloid or colloid) or high volume (≥2000 ml). The high volume group had significantly worse coagulation profile, required more blood products and had higher incidence of organ failure, although overall mortality was similar. These ‘iatrogenic’ factors are at least partially preventable after injury and ‘damage control resuscitation’ should be practised to minimize their effects [11].

**CLINICAL IMPORTANCE OF ACUTE TRAUMATIC COAGULOPATHY**

Every epidemiological study of ATC has confirmed the negative impact it has on trauma patient outcomes. Presence of this condition on hospital admission is independently associated with fourfold higher mortality and significantly greater transfusion requirements [12,13]. We have improved the resolution of that relationship with our observational study that identified a significant and dose-dependent increase in mortality and blood product requirements for trauma patients arriving in the emergency department with a PT ratio more than 1.2 [3**] (Fig. 1). The detrimental clinical effects of ATC also extend to the survivors. Maegle et al. [14] analysed the outcome of 8724 patients with severe multiple injuries and found that 29% of all patients with ATC developed multiorgan failure (MOF) within their later hospital course in contrast to only 12% in the group without (P < 0.001). The overall length of mechanical ventilation, ICU and hospital stay were longer in patients with coagulopathy versus those with normal haemostasis on admission (mechanical ventilation: 10 versus 6.5 days; ICU stay: 15 versus 11 days; hospital stay: 33 versus 26 days; all P < 0.001). Logically, ATC exacerbates blood loss in haemorrhaging trauma patients and rapid deliberate haemostatic normalization should improve outcomes. Robust studies demonstrating this are eagerly awaited.

**MECHANISMS OF ACUTE TRAUMATIC COAGULOPATHY**

Contemporary understanding of haemostasis recognizes that it is a dynamic equilibrium between procoagulant factors, anticoagulant factors, platelets,
endothelium and fibrinolysis. The timely redevelopment of diagnostic devices (e.g. thromboelastometry, platelet function testing, etc.) is supporting our expanding appreciation of trauma-associated haemostatic impairments. Endogenous systemic anticoagulation and fibrinolysis have emerged as probable mediators of ATC [15]. The clinical importance of fibrinolysis has been demonstrated by the dramatic survival benefit of blocking this pathway during haemorrhage [5]. Interest is now focused on the neglected components of coagulation such as platelets and endothelium, to better understand their role in this dysfunctional orchestra.

**PROCOAGULANT IMPAIRMENT**

The recent trend towards increased and earlier use of plasma for resuscitation of trauma-haemorrhage is contingent on the theory that coagulation per se (between factor VII-tissue factor complexing and stable fibrin polymerization) is acutely impaired after injury and that augmentation of this system should improve haemostasis, reduce blood loss and improve outcomes. However, despite a large number of retrospective reports of improved mortality with high ratios of plasma, there is scant evidence that coagulation factors are actually universally depleted in ATC, or that they are improved by high volumes of this product. Indeed, two recent studies have emerged that suggest thrombin generation may actually be enhanced after injury [16,17].

Historically, it is well documented that fibrinogen concentrations rapidly decline after injury and then rebound to supraphysiological levels in subsequent days [18,19]. Contemporary basic and clinical studies of ATC appear to confirm this. Various swine models of traumatic shock have demonstrated an acute reduction in circulating fibrinogen in association with poor clot strength on viscoelastic coagulation tests (VCTs), prior to fluid resuscitation [20,21]. It is not clear whether this is mediated purely by reduction in fibrinogen concentration or whether impaired stability is also functionally important. Johansson et al. [22] recently published a prospective observational study documenting acute haemostatic responses to trauma. Eighty patients who met ACIT3 inclusion criteria (adult direct hospital transfers within 2 h and receiving less than 2 l of intravenous fluid) were divided into coagulopathic (INR > 1.2 or activated partial thromboplastin time (aPTT) > 35) and non-coagulopathic cohorts. Those with ATC had significantly lower fibrinogen concentration (1.53 versus 2.54 g/l, *P* < 0.001). However, the relative contribution of hypofibrinogenaemia to their coagulopathy is debatable; concentrations above 1 g/l do not trigger specific replacement in most transfusion protocols [23]. Bigger studies with more comprehensive coagulation factor assessment are urgently required to justify the widespread empiric use of high plasma volumes. It may be that partial substitution with a concentrated source of fibrinogen (e.g. cryoprecipitate or fibrinogen concentrate), could be equally efficacious and reduce exposure to the harmful side-effects of plasma.

**SYSTEMIC ANTICOAGULATION**

We have previously proposed that systemic anticoagulation via activation of protein C may be a functional mediator of ATC [2]. Data from our murine model of trauma and haemorrhagic shock support this hypothesis [24]. This study assayed blood samples taken at the scene of injury and on arrival to the emergency room. Depletion of protein C in these samples was associated with prolongations of the PT and aPTT. Therefore, activation of protein C (with subsequent depletion) is mechanistically implicated in the pathophysiology of this coagulopathy. Interestingly, this also correlated with a specific reduction of circulating factor V activity, a target substrate of activated protein C (aPC). Johansson et al. [22] are the first group to record an increase in aPC concentrations after
injury. However, only 12 patients in this study were coagulopathic and it did not differentiate between those with and without ATC. Improved resolution of this association is expected with future studies.

**HYPERFIBRINOLYSIS**

Fibrinolysis is clearly a functional component of ATC. The impressive survival benefit associated with administration of tranexamic acid for traumatic haemorrhage highlights the pathological role of this antihaemostatic pathway after injury [5**]. Two recent prospective clinical studies have better defined the incidence and clinical importance of this entity. Tauber et al. [25*] performed ROTEM analysis on 334 major trauma patients (ISS > 15) upon admission to the emergency room and observed hyperfibrinolysis in 23, an incidence of 6.8%. In 14 cases, hyperfibrinolysis was considered fulminant with a complete breakdown of the clot observed within 60 min. A reduction of clot firmness by 16 and 35% was observed in another nine patients. The mortality rate in patients with fulminant hyperfibrinolysis was 85.7%, compared with 11.1% in low-grade fibrinolysis. Patients with hyperfibrinolysis had higher ISS, lower GCS, lower SBP and higher lactates than patients without hyperfibrinolysis. Kashuk et al. [26] performed TEG analysis on 61 major trauma patients with a median ISS of 32.5. Hyperfibrinolysis (>15% estimated clot lysis) was observed in 34% of the 32 patients who required a massive transfusion. Their risk of death was significantly higher and correlated with both the TEG G-value (negatively) and severity of fibrinolysis (positively).

**PLATELET DYSFUNCTION**

Platelet counts are mildly reduced by trauma and this appears to associate with poor outcomes. For example, Brown et al. [27*] performed a retrospective cohort study of 389 massively transfused trauma patients and reported that, in a logistic regression model controlling for ISS, GCS and admission base deficit, the odds of death at 24 h decreased by 12% for every 50 × 10⁹/l increase in platelet count. However, in most contemporary studies, they do not decline to levels that may be expected to contribute significantly to coagulopathy [22**,28]. Nevertheless, one or two reports have identified that a high ratio of platelets to packed red blood cells is associated with improved outcomes [29*]. This may lead us to conclude that the primary platelet impairment provoked by injury and/or haemorrhagic shock is functional. A single study of 163 trauma patients has recently reported a minor, but significant, difference in platelet aggregometry parameters (ADTtest and TRAPtest) between survivors and nonsurvivors [30*].

**ENDOTHELIAL ACTIVATION**

Vascular endothelium is an active participant in the pathophysiology of ATC. Large capillary beds host thrombomodulin and endothelial protein C receptors anchored through their luminal surface that capture thrombin and accelerate protein C activation 1000-fold [31]. In addition to inactivating coagulation factors Va and VIIIa, aPC also consumes plasminogen activator inhibitor-1 (PAI-1), the major antagonist of tissue-type plasminogen activator inhibitor-1 (t-PA). Consequently, traumatic haemorrhage with tissue hypoperfusion leads to overwhelming release of t-PA from vascular endothelial cells and subsequent hyperfibrinolysis [15].

Johansson et al. [32**,33*] have recently published fascinating data demonstrating an association between tissue hypoperfusion, neurohormonal activation and markers of endothelial disruption. In a prospective study of 75 adult trauma patients, circulating adrenaline levels were elevated in those with higher ISS, higher lactate and lower SBP. This correlated positively and independently with the incidence of ATC as well as levels of syndecan-1, histone-complexed DNA, high-mobility group box 1, soluble thrombomodulin, t-PA and D-dimers. Endothelial glycoalyx degradation is capable of triggering thrombin generation, protein C activation and hyperfibrinolysis. This is important because it indicates another potential mechanism by which tissue injury and shock mediate systemic anticoagulation early after injury.

**DIAGNOSIS**

Early diagnosis of coagulopathy in the bleeding trauma patient remains a challenge with no validated assays currently available that can reliably identify aberrant haemostasis in the acute phase [34,35,36*]. Laboratory-based clotting screens (PT, aPTT, fibrinogen) are conducted in platelet-poor plasma with inherent delays due to standard processing with results not being available to the treating clinician for 30–60 min [35,37**]. PT and aPTT provide only very limited details on early clot formation and neither can quantify the relative activity of procoagulants versus anticoagulants [38]. Platelet counts are typically normal in trauma and crucially are unable to identify or quantify the degree of platelet dysfunction secondary to the physiological derangement evident in TIC [8]. VCTs would appear to a viable and attractive alternative to conventional laboratory assays for the
rapid identification of ATC. Both TEG and ROTEM have minimal processing times, are performed in whole blood and rapidly evaluate the dynamics of clot formation and breakdown. Trauma patients with ATC (defined as PT ratio > 1.2) have a ‘signature’ thrombelastogram (Fig. 2). Compared to patients with PT ratio of 1.2 or less, the ATC trace is characterized by a reduction in clot strength with much smaller changes in laboratory clotting times and can be identified within 5 min – threshold of clot amplitude at 5 min (CAS) of 35 mm or less [37**]. Earlier animal and human studies comparing VCTs with coagulation screens have shown similar correlations. In a porcine model of hypothermia and haemorrhage, TEG was shown to be superior to conventional clotting assays in differentiating clotting abnormalities [21]. Doran et al. [39] showed, in a small study of combat casualties, that admission samples analysed by ROTEM were more sensitive than PT and aPTT in detecting laboratory-defined coagulopathy. PT/aPTT was abnormal in 21% of cases compared with 64% for ROTEM in patients who received a massive transfusion (>10 units of packed red blood cells). Of note, only 10% of patients who required a massive transfusion had prolongation of PT or aPTT that met diagnostic criteria for coagulopathy [PT > 18 s, aPTT > 60 s] [40].

The additional benefit of VCTs is their ability to detect and potentially aid the management of hyperfibrinolysis. Levrat et al. [41] reported evidence of hyperfibrinolysis with a concomitant increase in D-dimers within a small subgroup of coagulopathic trauma patients. They reported good correlation between euglobulin lysis times (a crude marker of clot breakdown) and ROTEM parameters of clot lysis at 30 min. Further studies have demonstrated an association between degree of clot lysis detected by ROTEM, injury severity and mortality [42*]. Fulminant hyperfibrinolysis (complete clot breakdown <30 min) can be detected early but intermediate or delayed hyperfibrinolysis may take 30–60 min to be visible. Further research is required to validate initial test parameters associated with hyperfibrinolysis and determine whether VCTs are able to serve as early triggers for antifibrinolytic therapy.

CONCLUSION

ATC is an endogenous impairment of all components of haemostasis. It develops rapidly in response to tissue injury and haemorrhagic shock and is exacerbated by hypothermia, acidosis and resuscitation with hypocoagulable fluids. Rather than being merely a consumptive coagulopathy, it is characterized by dysfibrinogenaemia, systemic anticoagulation, impaired platelet function and hyperfibrinolysis. There is undoubted potential to translate our developing knowledge of ATC pathophysiology into novel therapeutics capable of further reducing the mortality and morbidity associated with ATC. Further validation of haemostatic monitoring tools is essential to ensure that these are delivered in a targeted, efficient and cost-effective way.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 266–267).

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The first study to identify coagulopathy in trauma victims at the scene of injury. Important because it confirmed that ATC develops endogenously.
Trauma and transfusion


This study used data from a large trauma cohort (>5000 patients) to characterize the synergistic relationship between tissue injury and systemic hypoperfusion in the aetiology of ATC.


A large multinational placebo-controlled trial demonstrating a clinically relevant survival benefit of tranexamic acid during trauma haemorrhage. This drug should be part of every major haemorrhage protocol.


This study found that soldiers injured by explosion (with higher expected tissue injury load) had worse coagulopathies than a similar cohort injured by gun shot.


A useful observational study that uses a large retrospective cohort to identify the important variables independently associated with ATC (SSS, shock, hypothermia, high-volume fluids).


A novel study that indicates thrombin generation may actually be maintained acutely after injury. This is important because it would suggest that plasma may not be the optimal initial resuscitation product.


Report of a good quality swine model of ATC that identifies impaired fibrinogen and increased fibrinolytic activity after injury. Novel study demonstrating the clinical importance and pathophysiology of fibrinolytic activity after injury.


This study reports novel prospective data showing that diagnostic criteria for disseminated intravascular coagulation (DIC) has poor sensitivity for identifying trauma patients with acute haemostatic impairments.