# Acute coagulopathy of trauma: mechanism, identification and effect

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**Purpose of review**
Acute coagulopathy of trauma has only been described relatively recently. Developing early in the postinjury phase, it is associated with increased transfusion requirements and poor outcomes. This review examines the possible initiators, mechanism and clinical importance of acute coagulopathy.

**Recent findings**
Acute coagulopathy of trauma occurs in patients with shock and is characterized by a systemic anticoagulation and hyperfibrinolysis. Dilution, acidemia and consumption of coagulation proteases do not appear to be significant factors at this stage. There is evidence to implicate activation of the protein C pathway in this process. Diagnosis of acute coagulopathy currently relies on laboratory assessment of clotting times. These tests do not fully characterize the coagulopathy and have significant limitations, which reduce their clinical utility.

**Summary**
Acute coagulopathy results in increased transfusion requirements, incidence of organ dysfunction, critical care stay and mortality. Recognition of an early coagulopathic state has implications for the care of shocked patients and the management of massive transfusion. Identification of novel mechanisms for traumatic coagulopathy may lead to new avenues for drug discovery and therapeutic intervention.

**Keywords**
coagulopathy, massive transfusion, protein C, shock, trauma

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**Abbreviations**

| | |
|---|---|
| **PT** | prothrombin time |
| **PTT** | partial thromboplastin time |

## Introduction

Understanding of coagulation dysfunction associated with trauma has changed dramatically in the past 5 years and continues to evolve rapidly. The classical description of trauma associated coagulopathy views it as loss, dilution or dysfunction of the coagulation proteases. Loss is described as being due to bleeding or consumption, dilution is due to fluid administration and massive transfusion, while protease dysfunction is due to hypothermia and the effect of acidaemia on enzyme function [1]. Coagulation itself is still understood as a simple protease cascade and therapy is guided by clotting time tests developed in the 1940s for hemophilia.

While the clinical understanding and management of trauma coagulopathy has been fairly static, there has been an explosion in the science of haemostasis. The clotting cascade has been replaced by a cell-based representation of coagulation [2•] and there has been a renewed interest in the thrombotic control mechanisms (anticoagulant and fibrinolytic systems) and a new respect for the endothelium as an active driver of these processes [3]. New pharmaceutical agents that modulate haemostasis, including recombinant factor VIIa and activated protein C have been introduced into clinical practice. The utility of these agents has been limited by the lack of measurement tools to characterize coagulopathy and thus there is limited ability to determine the indications, timing or dose of administration. This has led to large-scale but ultimately equivocal clinical trials [4,5] and continued confusion regarding their use. Nevertheless, they have generated a renewed clinical interest in the role of the coagulation system in disease, and initiated a fresh examination of the pathophysiology and management of coagulopathy in trauma.

In 2003 we reported on a retrospective study of the admission coagulation results of 1088 trauma patients, prior to the administration of significant volumes of fluids or other intervention [6]. Nearly 25% of trauma patients arrived in the emergency department with a clinically significant coagulopathy. Patients with this acute coagulopathy of trauma were four times more likely to die than those without. The existence of this early coagulopathy has been verified by groups in Miami and Germany in subsequent studies, with remarkably similar results across over 20 000 patients, despite differences in the definition of coagulopathy (Table 1) [6,7,8•,9••,10•].

**Table 1 Summary of studies of acute coagulopathy of trauma**

| | Definition of coagulopathy | Number of patients | Percentage with coagulopathy | ISS | Mortality normal | Mortality coagulopathy |
|---|---|---|---|---|---|---|
| Brohi, 2003 [6] | PT >18 s or PTT >60 s | 1088 | 24% | 20[a] | 11% | 46% |
| MacLeod, 2003 [7] | PT >14 s or PTT >35 s | 10 790 | 28% | 9[a] | 6% | 19% |
| Maegele, 2007 [8•] | Quick test <70% | 8724 | 34% | 24[b] | 8% | 28% |
| Brohi, 2007 [9••] | PT >18 s or PTT >60 s[c] | 208 | 10% | 17[a] | 8% | 62% |
| Rugeri, 2007 [10•] | INR > 1.6 or PTT >60 s | 88 | 28% | 22[b] | n/a | n/a |

INR, International Normalized Ratio; ISS, Injury Severity Score; PT, prothrombin time; PTT, partial thromboplastin time.
[a] Median.
[b] Mean.
[c] For this review, data not presented in the original manuscript.

## Instigators of acute coagulopathy

Classically, trauma-induced coagulopathy is described as due to dilution, hypothermia, acidemia-associated dysfunction or consumption of coagulation proteases. None of these appears to be responsible for acute coagulopathy, and it appears that shock is the prime initiator of the process.

### Dilution

In each study, the time from injury to admission was relatively short at a median of 70–75 min. In the London study there was minimal prehospital fluid administration (median 500 ml) and we identified no relationship between fluid administration and the incidence of coagulopathy [6]. Higher volumes of fluid were given in the German study (mean 2200 ml) and there was a clear dilution effect, with coagulopathy present in more than 50% of patients who received more than 3 l of fluid in the prehospital phase [8•]. This may be a result of colloid use in this study as there appears to be little or no dilutional effect of crystalloid therapy on the standard tests of coagulation either *in vitro* [11] or in healthy volunteers [12]. Coagulopathy was still present, however, in 10% of patients who received less than 500 ml of fluid, suggesting an alternative mechanism is responsible.

### Hypothermia

None of the retrospective studies that identified early coagulopathy specifically reported patient temperature on admission. Moderate or severe hypothermia is present in less than 9% of trauma patients [13,14]. Although there is a relationship between hypothermia, shock and injury severity it remains a weak independent predictor of mortality (odds ratio 1.19) [14]. There is, however, very little effect of temperature on coagulation proteases at these temperatures, and significant effects on function and clinical bleeding are observed only at temperatures below 33°C [15–17].

### Acidemia

Acidemia affects the function of the coagulation proteases. Clinically it is difficult to separate the effects of acidemia per se and the effects of shock and tissue hypoperfusion. A recent study [18] examined the effects of intravenous administration of hydrochloric acid on human volunteers. While there was a definite dose–response effect of acidemia on clotting function as measured by thromboelastometry, clotting times were not prolonged. This is consistent with in-vitro studies for which there is little clinically significant effect on protease function down to a pH of 7.2 [16] and in animal studies for which a pH of 7.1 produces only a 20% prolongation of the prothrombin and partial thromboplastin times [17]. Whatever the exact effect of acidemia on coagulation function, it appears not to be reversible by simple correction of the acidosis [19,20].

### Consumption

Consumption of clotting factors has always been regarded as a primary cause of traumatic coagulopathy [1]. There is little evidence, however, to support consumption of clotting factors as a relevant mechanism for acute traumatic coagulopathy, and nothing to suggest a process of disseminated intravascular coagulation (DIC). There is certainly activation of the tissue-factor dependent extrinsic pathway and a linear relationship between thrombin generation and injury severity [9••]. In patients without shock, however, coagulation times are never prolonged, regardless of the amount of thrombin generated [9••]. Further, fibrinogen levels are rarely decreased in patients with acute traumatic coagulopathy [19]. A commonly held belief is that traumatic brain injury releases 'thromboplastins' into the circulation which then lead to a consumptive or DIC-like coagulopathy. Again, however, there is no evidence to support this, and we [21] and others [22] have refuted the presence of a specific brain injury-related coagulopathy.

### Hypoperfusion

Shock and tissue hypoperfusion is a strong independent risk factor for poor outcomes in trauma [23–26]. We have recently reported the results of a new study of acute coagulopathy investigating the effects of tissue hypoperfusion [19]. As mentioned above, no patient with a normal base deficit had prolonged prothrombin or partial thromboplastin times, regardless of injury severity or the

amount of thrombin generated. In contrast there was a dose-dependent prolongation of clotting times with increasing systemic hypoperfusion. Only 2% of patients with a base deficit under 6 mEq/l had prolonged clotting times, compared with 20% of patients with a base deficit over 6 mEq/l. Higher injury severity increased the incidence and severity of coagulopathy in shocked patients. Fibrinogen and platelet levels were normal in all patients. Shock and systemic hypoperfusion appears to be the key driver of acute traumatic coagulopathy.

## Mechanism of acute coagulopathy

Instead of being a dysfunction of the coagulation proteases, acute coagulopathy appears to be due to activation of anticoagulant and fibrinolytic pathways. The thrombomodulin–protein C pathway is implicated in these processes.

### Systemic anticoagulation through protein C activation

We have postulated that acute traumatic coagulopathy is due to systemic anticoagulation due to activation of the protein C pathway. In the above study, as hypoperfusion increased there was an increase in plasma levels of soluble thrombomodulin and a decrease in protein C levels [9••]. The magnitude of these derangements was increased by increasing injury severity and thrombin generation but never occurred in the absence of hypoperfusion. Theoretically then, in the absence of hypoperfusion, trauma activates the extrinsic pathway, ultimately generating thrombin, which cleaves fibrinogen to form fibrin (Fig. 1). In the presence of tissue hypoperfusion, however, 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 protein C, which inhibits the extrinsic pathway through cofactors V and VIII (Fig. 1).

We were not able to measure activated protein C levels in this study due to the assay's complexity at the time. The activation of protein C, however, was strongly suggested by a dose-dependent prolongation of clotting times as protein C levels fell below normal. Corroborating this, we found that in the presence of hypoperfusion and increased levels of thrombomodulin, fibrinogen levels remained normal, indicating that less thrombin was available to cleave fibrinogen (as it was complexed to thrombomodulin). Nevertheless, confirmation of the generation of activated protein C in hypoperfusion is required to verify this hypothesis. Intuitively, however, it seems appropriate that tissues subjected to low-flow states should generate an anticoagulant milieu to avoid thrombosis of vascular beds. This necessary biological response becomes pathological in the presence of shock with systemic hypoperfusion following major trauma.

### Hyperfibrinolysis

Trauma is associated with increased fibrinolytic activity. Raised D-dimer levels following injury have been identified in many studies [9••,27]. Activation of fibrinolysis occurs as tissue plasminogen activator (tPA) is released from the endothelium following injury and ischemia [28–30]. This is a local control mechanism to reduce propagation of clot to normal vasculature, and our study was consistent with these findings [9••]. We also, however, identified a reduction in plasminogen activator inhibitor-1 (PAI-1) levels in patients with tissue hypoperfusion, who had almost twice the levels of tPA than

**Figure 1 Anticoagulation**

Thrombin is generated primarily via the 'extrinsic' pathway with multiple feed-forward loops. When thrombomodulin (TM) is presented by the endothelium, it complexes thrombin which is no longer available to cleave fibrinogen. This anticoagulant thrombin activates protein C which reduces further thrombin generation through inhibition of cofactors V and VIII.
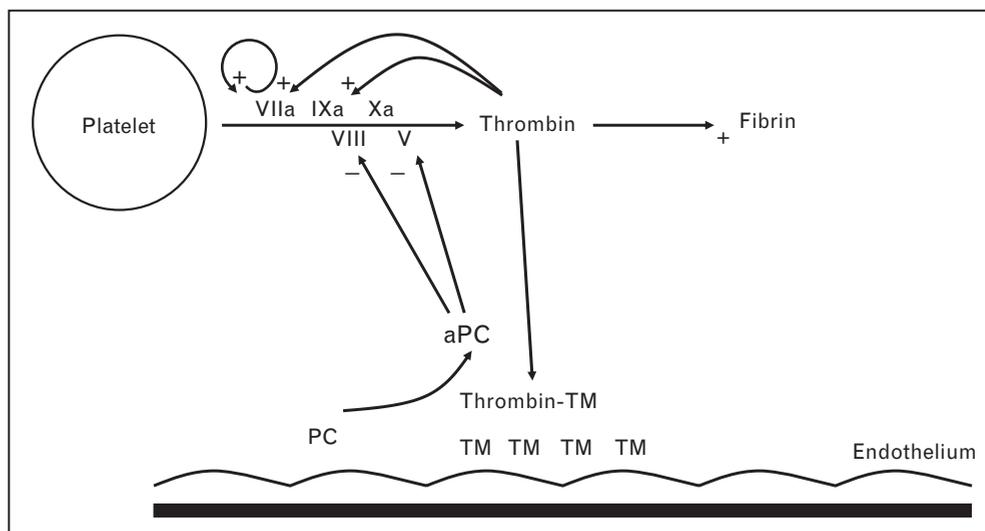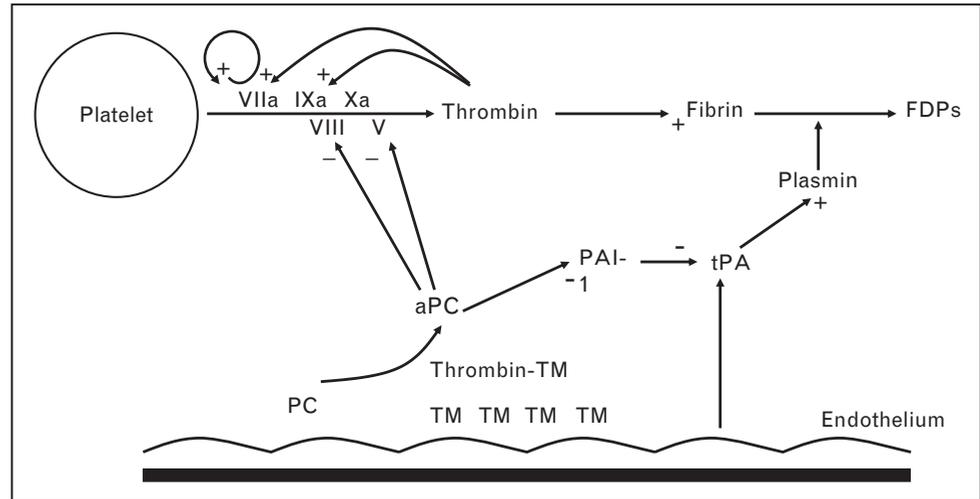
**Figure 2 Hyperfibrinolysis**

Tissue plasminogen activator (tPA) is released from the endothelium by injury and hypoperfusion and cleaves plasminogen to initiate fibrinolysis. Activated protein C (aPC) consumes plasminogen activator inhibitor-1 (PAI-1) when present in excess, and reduced PAI-1 leads to increased tPA activity and hyperfibrinolysis.



patients without shock. Activated protein C in excess will consume PAI-1 [31] and thus lead to a 'de-repression' of fibrinolytic activity and systemic hyperfibrinolysis (Fig. 2).

Thus acute coagulopathy of trauma is initiated by hypoperfusion and is characterized by systemic anticoagulation and hyperfibrinolysis. There is strong evidence to implicate endothelial presentation of thrombomodulin and thrombin activation of protein C in the development of this pathophysiological state. Further studies are required to confirm this, but the possibility of new therapeutic targets for intervention is enticing.

## Diagnosis of acute coagulopathy

The retrospective studies which identified the presence of an early coagulopathy of trauma all used variants of the prothrombin time (PT) and partial thromboplastin time (PTT) for diagnosis [6,7,8•,9••]. More patients have an abnormal PT than PTT, but the PTT appears to be more specific for predicting outcome. In the Miami study, 28% of patients had an abnormal PT compared with 8% of patients with an abnormal PTT [7]. An abnormal PTT, however, had an adjusted odds ratio of death of 4.26, compared with 1.54 for an abnormal PT [7]. In our study the PTT correlated better with low protein C levels than the PT, which is expected from the inhibitory effect of activated protein C on both factors V and VIII [9••].

There are problems with using these clotting times for the diagnosis of acute coagulopathy. Laboratory analysis of PT and PTT takes 20–60 min in most trauma centers. Whether near-patient tests of PT and PTT are accurate in trauma and haemorrhage is as yet unknown. More importantly, these tests describe only the first 20 and 60 s of clot formation: a process which is probably not complete for 15–30 min. There is no assessment of clot quality or strength, fibrinolytic activity or platelet function. Further, as the old concepts of the extrinsic and intrinsic pathways have been discarded, it is now no longer clear what derangements of the coagulation network these tests are measuring.

Thromboelastometry has been used in clinical practice for many years, but only recently has equipment become robust and stable enough for its use to be extended into the resuscitation room. A recent study [10•] reported on rotational thromboelastometry (RoTEM) findings in early traumatic coagulopathy. The study was designed to validate the RoTEM results against the standard tests of coagulopathy and samples drawn on admission were pooled with samples drawn at 6, 12 and 24 h for analysis. While the study showed that thromboelastometry is feasible in early trauma it is difficult to draw further conclusions about the characterization of acute coagulopathy from these results.

There has been a single study of platelet function in trauma patients [32]. It is difficult to interpret these results in light of our current knowledge of early coagulopathy. Overall there was an increase in platelet function but nonsurvivors showed a decrease in platelet function compared with controls. Again, platelet count was normal on admission. Although more research is needed to fully characterize acute coagulopathy it is clear that these functional tests show that the routine tests of clotting time miss many important defects of coagulation in trauma patients. Whether they are useful for diagnosis or guiding therapy is also yet to be determined.

## Clinical significance and implications

Presenting to the emergency department with an established coagulopathy has a significant impact on patient outcome, and the discovery of a new initiator and possible mechanism has several important implications for clinical practice and further research.

### Outcomes

Patients who arrive in the emergency department with a coagulopathy are three to four times more likely to die [6,7,8•,9••] and eight times more likely to die within the first 24 h [8•]. Coagulopathy remains an independent predictor of death in multivariate analyses including injury severity and degree of shock, although there is clearly some interdependence between these variables [7]. PTT is a better predictor of mortality than PT (adjusted odds ratio 4.3 versus 1.4) [7]. High plasma soluble thrombomodulin is associated with an odds ratio of death of 2.5 and low protein C with an odds ratio of 6.2 [9••].

Coagulopathy on admission is associated with longer intensive care and hospital stays. Patients are more likely to develop acute renal injury [9••] and multiple organ failure [8•], have fewer ventilator-free days [8•,9••] and there is a trend to an increased incidence of acute lung injury [8•].

### Transfusion requirements

Unsurprisingly, patients with an acute coagulopathy have increased transfusion requirements in the first 24 h of admission. In our hypoperfusion study, patients with a coagulopathy on admission (PT or PTT >1.5 times normal) received a mean of 10 units of blood, compared with 2 units for those with normal clotting times. Low protein C or high thrombomodulin levels were also associated with increased transfusion requirements [9••].

These findings have yet to be transferred into clinical practice, as most protocols for the administration of coagulation factor therapy in bleeding trauma patients are reactionary and prescribe fresh frozen plasma after massive transfusion [33]. There are emerging retrospective data from the US military that earlier and more aggressive treatment of acute coagulopathy is beneficial, leading to the concept of 'damage control resuscitation' [34].

Although these strategies would appear intuitively to make sense, aggressive augmentation of thrombin generation in the presence of shock may be counterproductive. If our hypothesized mechanism is correct, while there is systemic hypoperfusion the endothelium will continue to present thrombomodulin. More thrombin generation will lead to increased activation of protein C. Initially, high-dose fresh frozen plasma or recombinant factor VIIa therapy may overwhelm the thrombomodulin receptors and lead to increased clot formation. Activated protein C, however, has a relatively long half-life [35], and there may be a delayed rebound coagulopathy associated with re-bleeding. Further research is needed to determine the effect of these aggressive protocols. Until then, early definitive haemorrhage control followed by aggressive correction of tissue hypoperfusion is the key step in terminating acute traumatic coagulopathy.

### Late hypercoagulability and thrombosis risk

Several intensive care studies have identified a late hypercoagulable state in trauma patients [36–38] and trauma patients are known to have an increased risk of thromboembolic complications [39]. An early study investigating risk factors for the development of venous thromboembolism in trauma patients identified the presence of a coagulopathy on admission as a strong independent predictor [40]. Part of the explanation for this may lie in the early activation of protein C resulting in protein C depletion. As protein C is synthesized in the liver, it will take several days for protein C levels to return to normal, during which time a hypercoagulable state will exist that is known to predispose to venous thrombosis. Patients who present with coagulopathy should be considered at increased risk of deep venous thrombosis and pulmonary embolism and receive prophylaxis accordingly.

### Sepsis

As well as being involved in coagulation, protein C plays a central role in inflammation [41•], and patients with severe sepsis have low protein C levels [42]. Trauma patients receiving massive transfusions have an increased incidence of sepsis [43] and it is interesting to conjecture that the low protein C levels seen in both conditions may be the result of systemic hypoperfusion and early activation (and so depletion) of protein C. This also suggests a possible indication for delayed restoration of protein C levels in trauma patients with early coagulopathy and reduced protein C levels.

## Conclusion

The past 5 years have seen a renewed interest in traumatic coagulopathy and we are at the beginning of an explosion of research into its nature, effects and management. The coagulopathy of trauma is due to shock with systemic hypoperfusion and the protein C pathway is implicated in its mechanism. Patients presenting to the emergency department with an established coagulopathy are liable to poor outcomes, and must be recognized as early as possible and managed directly and aggressively. Exactly how to achieve this will be the subject of major basic, translational and clinical research programmes over the next decade.

# References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 763).

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