The ‘procoagulopathy’ of trauma: too much, too late?

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Purpose of review
Although early acute traumatic coagulopathy has received much recent attention, the procoagulopathy that often follows appears less appreciated. Thromboembolic disease following trauma is common and lethal, but very effective prophylactic strategies are available. These strategies are variably implemented because of the difficulty in quantifying the magnitude of procoagulopathy in individual patients.

Recent findings
The principal mechanisms of the procoagulopathy of trauma include inflammation and disseminated intravascular coagulation, tissue factor and thrombin dysregulation, and circulating microparticles and phospholipids. Quantification of these factors may allow better risk assessment in individual patients, but as yet none of these tests is in routine practice. Viscoelastic measurement of developing clot strength identifies a procoagulant state in many trauma patients, and may be a guide to the best choice of the many options for thromboembolic prophylaxis.

Summary
The logical next step following from the improved pathophysiological understanding of the procoagulopathy of trauma should be a simultaneous clinical trial of procoagulopathy diagnosis and thromboembolic prophylaxis.

Keywords
blood coagulation disorders, disseminated intravascular coagulation, trauma, wounds and injuries

INTRODUCTION
Trauma produces time-dependent responses from the haemostatic system that can increase risk of bleeding soon after injury and, later, increase the risk of thrombosis. Coagulopathic bleeding in trauma is a substantial problem. The US military found 15% of modern battlefield traumatic deaths are potentially preventable, and that 80% of preventable deaths were due to haemorrhage [1]. Up to 25% of severe trauma patients arrive at hospital with an established coagulopathy [2–4], making haemorrhage control more difficult. Early coagulopathy is caused by hypoperfusion and tissue injury resulting in thrombomodulin expression, activation of protein C, and hyperfibrinolysis [3,5]. Clearly, attenuating early coagulopathy is important, and administration of plasma and platelets [6,7], concentrated clotting factors such as fibrinogen and prothrombin complex concentrate [8], and tranexamic acid [9], with varying degrees of certainty, appears useful in reducing mortality.

Although much has been written on the acute coagulopathy of trauma, less understood is the hypercoaguable state that often subsequently develops. The procoagulant treatments listed above may accentuate this condition. While recently deployed to Afghanistan, anecdotally, we have noticed an entity of ‘hyperacute venothromboembolic disease’ occurring as early as 6 h following massively destructive tissue trauma. In light of the high incidence of thromboembolic disease in survivors of traumatic haemorrhage described below, along with the poorly-characterized delayed effects of novel approaches to control bleeding, it is important to
consider the concept of a ‘procoagulopathy’ of trauma. This review focuses on what is known of the epidemiology, pathogenesis, and clinical implications of this concept, culminating in a suggestion for the type of research that would resolve considerable uncertainty and controversy.

EPIDEMIOLOGY OF THE PROCOAGULOPATHY OF TRAUMA

The incidence of deep venous thrombosis (DVT) associated with major trauma is variably reported in database studies as 1.8 [10] to 5.1% [11*], with clinical trials enrolling higher risk patients finding rates of 11.5 [12] to 44% [13] despite thromboprophylaxis. Military casualties (with predominantly penetrating blast-fragmentation wounds) may be at particularly high risk [14]. This wide variation is explained not only by the population studied but also the intensity of diagnostic screening [15,16]. Venous thrombosis is complicated by pulmonary embolism in at least 3.2% of trauma patients [17], with a pulmonary embolism fatality rate approaching 50% [18]. Pulmonary embolism is the third leading cause of death among patients who survive the first 24 h after trauma [19,20]. Asymptomatic pulmonary embolism detected on screening appears more common (24% on one small series) [21]. Pre-disposing factors include age 40 years or more, extremity or head injury, 3 or more days requiring mechanical ventilation, venous injury, and major surgery [16], to which a recent review added spinal cord injury, lower extremity and pelvic fractures, need for surgical procedures, femoral venous line insertion, prolonged immobility, longer hospital stay, trauma severity, and mechanism of injury [22**]. Although the Wells scores are commonly used in a general patient population to predict risk of DVT [23] and pulmonary embolism [24], these appear less relevant in trauma [25]. No trauma-specific risk prediction system is in general use. As various effective thromboprophylaxis strategies exist but are often avoided because of the risk of bleeding, such a risk model seems overdue.

REGULATION OF COAGULATION

The coagulation response is regulated to ensure timely thrombus formation without an overshoot of fibrin generation (Fig. 1) [26]. Once the injured endothelium is isolated from blood, fibrin formation not only ceases, but plasm-in-mediated fibrinolysis ensues. Plasmin is formed from plasminogen by tissue plasminogen activator, the principal inhibitor of which is plasminogen activator inhibitor (PAI-1). Protein C, converted to activated protein C (APC) by thrombin bound to thrombomodulin on the endothelial cell membrane, is a second important regulator of both haemostasis and inflammation. APC serves as an anticoagulant by inhibiting activated coagulation factors VIII and V, and also exhibits a profibrinolytic function by inhibiting PAI-1 [27]. Tissue factor pathway inhibitor and antithrombin III are also important regulatory components, described below.

PROCOAGULANT MECHANISMS IN TRAUMA

The high incidence of thromboembolic disease after major trauma suggests that, at least in some patients, these idealized regulatory mechanisms can fail. Several mechanisms seem to act together to produce the procoagulant tendency in the subacute phase of trauma: inflammation and disseminated intravascular coagulation (DIC); tissue factor and thrombin dysregulation; and circulating microparticles and phospholipids.

Disseminated intravascular coagulation due to inflammation

Failure of haemostatic regulation accompanies many forms of critical illness, resulting in DIC [28]. Contributing components to DIC include increased tissue factor expression, suboptimal function of natural anticoagulant systems, dysregulation of fibrinolysis, and increased anionic phospholipid availability [29]. There is some debate over whether DIC occurs in the acute phase of trauma. DIC involves the consumption of clotting factors, characteristically leading to elevation of traditional
Tissue factor

Tissue factor (TF) III is the central initiator of cell-based coagulation following trauma [36,37]. TF acts as the cellular receptor for FVIIa, with the TF:FVIIa complex initiating coagulation by activating FX, which combines with FV to convert prothrombin (FII) to thrombin (Fig. 3). The small quantity of thrombin generated during this initiation phase is critical to subsequent clot amplification and propagation (Fig. 4), but these phases occur only once the tissue defect is sufficient for platelets and larger proteins to exit the vasculature and complex with TF-bearing extravascular cells [28].

Under normal conditions, TF is probably not expressed on cells in direct contact with the blood, such as vascular endothelial cells [38], but is upregulated and expressed in response to vascular injury, circulating inflammatory mediators and hypoxia [39]. Monocytes and macrophages express TF after stimulation, primarily by inflammatory cytokines. TF also circulates bound to microparticles, described below. This pathological expression of TF may trigger delayed pathological thrombosis.

Tissue factor pathway inhibitor (TFPI), synthesized by endothelial cells and released after thrombin stimulation, is the major downregulator of the
FIGURE 2. The extensive ‘cross talk’ in haemorrhagic shock procoagulopathy and thrombosis are the result of a process that begins with haemorrhage and coagulopathy.

FIGURE 3. Initiation of coagulation. The result of the initiation phase of coagulation is the generation of a small quantity of thrombin, which is the starting point for the amplification phase. FVa, activated factor V; TF, tissue factor (etc.).
Thrombin, thrombomodulin, and antithrombin

Thrombin (FIIa) is the central product of the initiation phase of coagulation. This enzyme uniquely displays procoagulant, anticoagulant, fibrinolytic, and cellular effects. These various functions and their timings are critical to normal haemostasis or indeed the potential for thrombosis [43].

The relationship between the amount of thrombin generated following injury and clinical effect is complex. At the high levels produced by a functioning coagulation cascade, thrombin is the critical enzyme producing fibrin. However, in the presence of excess thrombomodulin, thrombin becomes functionally anticoagulant [27], fundamental to the pathogenesis of the acute coagulopathy of trauma [44]. Downregulation of thrombomodulin expression could logically be a mechanism for procoagulopathy. Thrombomodulin expression usually increases in sepsis [45] and acute respiratory distress syndrome [46], but surprisingly the trauma of lung resection caused thrombomodulin to fall in comparison with controls [47]. The association of traumatic thromboembolic disease and thrombomodulin levels is yet to be determined.

Antithrombin III (ATIII) is an important inhibitor of thrombin [48]. ATIII activity is decreased in patients with trauma, shock, and sepsis as a result of degradation by granulocyte elastase and consumption during complex formation with other coagulation factors [49]. An increase in serum elastase due to trauma or sepsis may promote intravascular...
thrombosis by the inhibition of ATIII at the blood–endothelial cell interface. Trauma patients with an acute coagulopathy had dysregulated haemostasis, characterized by generation of excessive nonwound-related thrombin. These findings were attributed to a combination of stimulatory circulating procoagulants and depressed levels of ATIII allowing unchecked systemic thrombin generation to occur [50].

**Microparticles containing tissue factor and phospholipids**

Microparticles are highly procoagulant vesicles derived from either activated or apoptotic budding from cell membrane surfaces of platelets, leukocytes, erythrocytes, and endothelial cells in both physiological and pathological conditions [51]. Microparticle levels increase in response to platelet activation, endothelial injury, cell surface thrombin activity, or with complement activation [52]. Testa-

ment to their critical role in haemostasis is that a defect in the ability to form microparticles results in a severe bleeding disorder (Scott syndrome) [53]. Following trauma and vessel wall injury, cellular TF triggers clotting but is then excluded from clot propagation by the developing thrombus. Circulating microparticles containing TF may provide an alternative source of TF to facilitate continued thrombus formation [54]. The procoagulant state in patients after cardiopulmonary bypass may be partly because of increased microparticle tissue factor activity [55]. Circulating thrombogenic microparticles and plasma procoagulant activity were elevated in patients with traumatic brain injury [56], and in blunt trauma microparticles correlated with injury severity [57**].

Anionic phospholipids, such as phosphatidyl-

serine, are located in the inner monolayer of the normal plasma cell membrane. During the ‘budding off’ of a microparticle, this classical structure is lost, with ionic phospholipids being transferred to the outer membrane of the microparticle. Phosphatidyl-

serine profoundly increases the procoagulant activity of microparticles by allowing the surface assembly of clotting components [58]. Platelets appear to be the major source of the phosphatidyl-

serine microparticles in blood, which represent 70–90% of all circulating microparticles [59].

**CLINICAL IMPLICATIONS**

The procoagulopathy of trauma appears relatively common, is frequently lethal, and its pathogenic mechanisms are at least partly understood. What are the implications for clinicians?

**Diagnosis of the procoagulant state**

The complexity and dynamic nature of the anti and procoagulant balance in trauma make it difficult to reliably identify risks or optimal therapy in individual patients. Biomarkers of platelet and endothelial activation such as P and E-selectin may facilitate early tailored thromboembolism chemoprophylaxis. Of the mechanisms postulated above, quantification of microparticles is promising but awaits standardized protocols for quantification and epidemiologic studies to determine threshold levels warranting intervention [60*]. Of currently available test methods, point-of-care rotational viscoelastic measurement of clot development using thromboelastography (TEG) or thromboelastometry (ROTEM) allows for assessment of time to initial fibrin formation, maximal clot strength, and subsequent fibrinolysis [61]. Described in more detail by Keene et al. [62] in this volume, TEG and ROTEM use whole blood and so incorporate information on platelet function, avoiding potentially misleading measures obtained from analysis of soluble clotting factors in isolation. TEG found 65% of 69 blunt trauma patients were hypercoagulable at the time of evaluation. In nonbleeding trauma patients, TEGs showed an overall hypercoagulable state for the first 7 days following injury that was not reflected in PT or aPTT [63]. The value of TEG in the management of the acute traumatic coagulopathy has become established in the military [62]. A logical, but as yet unproven, extension would be to assess whether TEG or ROTEM can reduce thromboembolic complications by better directing thromboprophylaxis.

**Surveillance for thromboembolic complications**

The characteristics of various tests to detect venous thromboembolic disease are well known, but their optimal timing is not. Clinical examination is unreliable, with 85% of DVTs diagnosed using screening ultrasound in high-risk patients not suspected on clinical grounds [64]. Measurement of blood d-dimer concentrations, of some use in other patient groups [65], is less useful in trauma because of raised levels produced by systemic inflammation in the absence of thromboembolism [66]. The possible utility of redefining values at which more specific tests or therapy might be warranted is unknown. Many clinicians perform ‘surveillance’ duplex ultrasound in patients at highest risk for DVT, but the pretest probability that provides the optimal cost-benefit ratio from this approach is not well characterized. Practice is highly varied [67]. American College of Chest Physicians (ACCP) Guidelines [68**] recommend against Doppler ultrasound in
asymptomatic patients, whereas the Eastern Association for the Surgery of Trauma (EAST) Practice Management Guidelines [69] recommend that screening asymptomatic high-risk patients may be clinically and cost-effective. Routine surveillance for pulmonary embolism might be considered even less valuable, as clinically significant pulmonary embolism should produce clinical features that would allow a more targeted approach. However, like DVT, most pulmonary embolisms in critical illness are not apparent from clinical signs [21]. Early detection of small, haemodynamically insignificant pulmonary embolisms might prevent a subsequent fatal event, or might precipitate treatment worse than the disease [70]. Ventilation-perfusion scanning is not very useful in trauma, as many patients have radiographic abnormalities that preclude its use. In one observational series, this technique was hardly ever used [17]. Although computerized tomography-pulmonary angiography is overwhelmingly (81 [71] to 97% [17]) the most commonly used modality to diagnose pulmonary embolism, it carries a 10–20% risk of contrast-induced nephropathy [72]. Increasingly, routine use and improved skill with echocardiography holds the greatest promise for earlier diagnosis of pulmonary embolism in trauma.

**Implications of procoagulant medications**

The various components of ‘haemostatic resuscitation’ (clotting factors; hypotensive resuscitation; tranexamic acid) improve mortality, but less is known of their impact on the subsequent procoagulopathy of trauma. The CRASH-2 trial of tranexamic acid [9] reported rates of DVT and pulmonary embolism of 0.4% and 0.7%: implausibly low given higher rates in similar populations. Conducted primarily in the developing world, thromboembolic complications in CRASH-2 were probably infrequently actively sought, which is likely to be the explanation for the higher rate of pulmonary embolism than DVT. The incidence of prothrombotic complications in the many retrospective studies comparing high vs. low ratios of plasma and platelets to red cell transfusion is generally not reported. The currently underway PROPR trial (NCT01545232) may answer this question. For now, in a vacuum of evidence, it would seem wise for clinicians to have a greater vigilance for thromboembolic complications in patients who survive their haemostatic resuscitation.

**Thromboprophylaxis: alternatives**

There are various alternatives for thromboprophylaxis in patients at high risk for the procoagulopathy of trauma. A 2013 Cochrane review [22**] analysed a total of 16 trials involving 3005 trauma patients, finding that prophylaxis (of any sort) nearly halved the rate of DVT. Although mechanical prophylaxis is effective, it is about half as effective as heparin, and low molecular weight heparin (LMWH) is superior to unfractionated heparin. Most effective is a combination of mechanical and pharmacological prophylaxis. Surprisingly, there was no evidence that thromboprophylaxis reduces mortality or pulmonary embolism.

Quantifying reductions in DVT answers only half of the question in trauma, as when the risk of death from bleeding becomes less than the risk of thromboembolic disease is difficult to identify in an individual patient. The two most important guidelines ‘sit on the fence’: the ACCP guidelines recommend patients with poorly defined ‘increased risk of bleeding’ (previous major bleeding; renal failure; requirement for an antiplatelet agent; and surgical factors) have no pharmacologic prophylaxis [68**], and the EAST guidelines recommend that in ‘patients in whom bleeding could exacerbate injuries . . . the safety of low-dose heparin has not been established, and an individual decision should be made when considering anticoagulant prophylaxis’ [69]. Although the EAST guidelines acknowledge the greater risk and efficacy of LMWH, their recommendation that this be used for all trauma patients with an ISS greater than 9 ‘who can receive anticoagulants’ does not provide the clinician with definitive advice.

Alternatives to heparin prophylaxis include compression stockings and intermittent pneumatic devices that compress the lower leg or move the foot. Not only is the efficacy of these devices inferior to heparin [22**], they can be impossible to apply to a patient with lower limb trauma. Some argue very high-risk patients warrant insertion of prophylactic inferior vena cava filters: for example, the EAST guidelines recommend ‘consideration’ in very high thromboembolism-risk patients who cannot receive other pharmacological prophylaxis for 5–10 days after injury because of intracranial haemorrhage, ocular injury, solid organ injury, or retroperitoneal haemorrhage, or who have particularly high thromboembolism-risk injury patterns: severe head injury, incomplete spinal cord injury, pelvic fractures with long bone fractures, or multiple long bone fractures [69]. In contrast, the ACCP guidelines recommend against inferior vena cava filters for primary prevention [68**].

**Thromboprophylaxis: when to commence pharmacological prophylaxis?**

Lack of guideline consensus on when to start prophylactic heparin is reflected in highly variable clinical practice [73]. Commencing heparin once
bleeding risk has normalized misses the main period of procoagulopathy. Failure to resolve this question despite many studies suggests the need for a different approach. Logically, given the heterogeneity of trauma patients, a diagnostic test for procoagulopathy that could more accurately predict thrombotic risk could end this confusion.

CONCLUSION
Predicting thrombotic or haemorrhagic episodes following trauma and developing targeted approaches for minimizing these events require an understanding of both the coagulopathy of trauma and the procoagulopathy that commonly follows. The evolution of this field will hopefully see better diagnostic tests for procoagulopathy based on the pathophysiological mechanisms outlined here. Based on epidemiological studies to allow sensible interpretation of test results, clinical trials simultaneously testing diagnostic and prophylactic strategies will be required. Clinical trials simultaneously testing a diagnostic and therapeutic strategy (‘theranostics’) are becoming increasingly accepted. For now, the simple recognition and clinical acknowledgement of a ‘procoagulopathy of trauma’ is a step in the right direction.

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Conflicts of interest

Commander Holley and Lieutenant Colonel Reade are serving officers in the Australian Defence Force. No financial or academic conflicts of interest are reported.

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


This is the most comprehensive systematic review of the effectiveness of various strategies for the prevention of thromboembolic disease in trauma.


This is an excellent review of the most promising diagnostic markers for thromboembolic disease.


This is a case–control study of 52 blunt injured patients and 19 controls that identified markers for deep vein thrombosis.

Practice Guidelines. Chest 2012; 141:e278S–e325S.

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