Journal of Veterinary Emergency and Critical Care

Clinical Practice Review

Journal of Veterinary Emergency and Critical Care **24**(1) 2014, pp 63–74
doi: 10.1111/vec.12130

Traumatic coagulopathy-Part 1: Pathophysiology and diagnosis

Lee Palmer, DVM, DACVECC and Linda Martin, DVM, MS, DACVECC

Abstract

Objective – To review the current literature in reference to the pathophysiology and diagnostic modalities available for acute traumatic coagulopathy (ATC) in relationship to traumatic hemorrhagic shock.
Etiology – Posttraumatic hemorrhage is responsible for one of the leading causes of preventable human deaths worldwide. Acute traumatic coagulopathy is an endogenous hypocoagulable condition that has been observed during the immediate (< 1 hour) posttraumatic period. Phenotypically, ATC manifests as a state of systemic hypocoagulability and hyperfibrinolysis. Although different functional mechanisms have been proposed for causing ATC, it is universally thought to be a manifestation of severe tissue injury, shock-induced hypoperfusion, systemic inflammation, and endothelial damage. Excessive activation of the thrombin-thrombomodulin activated Protein C pathway, catecholamine-induced endothelial damage as well as disseminated intravascular coagulation (DIC) with a fibrinolytic phenotype are all hypotheses that have been proposed in attempts to explain the functional mechanism of ATC.
Diagnosis – An accurate and reliable test remains to be validated for ATC. Traditional coagulation assays (activated partial thromboplastin times and prothrombin times) along with platelet count and fibrinogen concentrations have been used more commonly. Viscoelastic tests (thromboelastography and rotational thromboelastometry) are currently being investigated as a more predictive modality for identifying and guiding therapy for ATC.
Therapy – Damage control resuscitation and hemostatic resuscitation are gaining favor as the optimal resuscitative strategies for hemorrhagic shock and ATC. Antifibrinolytics may also play a role when hyperfibrinolysis is present.
Prognosis – Massive hemorrhage accounts for 30–56% of prehospital posttraumatic deaths in people, with coagulopathic hemorrhage remaining one of the major causes of preventable deaths within the first 24 hours posttrauma. Ten to twenty-five percent of human trauma patients experience ATC, which has been shown to prolong hemorrhage, deter resuscitative efforts, promote sepsis, and increase mortality by at least 4-fold. Prognosis in veterinary patients is not currently known.

(J Vet Emerg Crit Care 2014; 24(1): 63–74) doi: 10.1111/vec.12130

Keywords: coagulopathy, fibrinolysis, protein C, shock, trauma

Introduction

Posttraumatic hemorrhage still remains one of the leading causes of human deaths.[1,2] Massive hemorrhage accounts for 30–56% of prehospital posttraumatic deaths[1,2] whereas coagulopathic hemorrhage remains one of the major causes of preventable deaths within the first 24

From the Department of Clinical Sciences, College of Veterinary Medicine, Auburn University, Auburn, AL 36849.

The authors declare no conflict on interests.

Address correspondence and request for reprints sent to
Dr. Palmer, Department of Clinical Sciences, College of Veterinary Medicine, Auburn University, 612 Hoerlein Hall, Auburn, AL 36849.
Email: lep0011@auburn.edu
Submitted July 9, 2012; Accepted November 7, 2013.

Abbreviations

ATC	acute traumatic coagulopathy
aPTT	activated partial thromboplastin time
BD	base deficit
DIC	disseminated intravascular coagulation
FDP	fibrin degradation product
MODS	multiorgan dysfunction syndrome
ISS	injury severity score
INR	international normalization ratio
PT	prothrombin time
ROTEM	rotational thromboelastometry
TEG	thromboelastography
TASH	trauma associated severe hemorrhage

hours posttrauma.[3–8] Forty to seventy percent of human trauma-related deaths occur within the first few minutes to 6 hours postinjury[8] with massive hemorrhage (blood loss > 30–40% of total blood volume blood) and severe brain injury being responsible for the majority of these deaths. Mortality (~10–30%) that occurs over the subsequent 24 hours postinjury is primarily attributed to ongoing hypoxia, hypovolemia, ongoing internal hemorrhage, coagulopathy-induced blood loss, or cardiovascular and respiratory failure. If patients survive the initial 24 hours they may subsequently experience sepsis, multiple organ dysfunction syndrome (MODS), and ultimately death days to weeks following the initial insult. Clinical and laboratory experience has demonstrated that aberrations in the coagulation system play an integral role in mediating early (< 24 hours) and late (> 24 hours) posttraumatic deaths. A posttraumatic coagulopathy potentiates early deaths through prolongation of bleeding and sustainment of hypoperfusion. Late deaths arise from coagulation's ability to modulate the immuno-inflammatory response that eventually leads to the development of acute lung injury, sepsis, and MODS.[9–11]

It is now recognized that activation of the coagulation cascade is a common sequel following trauma and shock where the severity of injury and degree of shock appears to be positively correlated to the degree of coagulopathy.[12–14] The presence of traumatic coagulopathy has been shown to be an independent risk factor for death[9] where human trauma patients presenting with a coagulopathy on arrival to the hospital suffer a poorer outcome and up to a 4-fold higher risk for developing MODS and death.[12–14] Although not fully elucidated, mechanisms responsible for this traumatic coagulopathy are multifactorial and time-sensitive in nature and appear to involve interactions between all components of the hemostatic and inflammatory systems.

In people, it has been reported that up to 25–34% of trauma patients suffering major injuries and significant hemorrhage are hypocoagulopathic upon presentation.[13–15] In addition, it has also been shown that this acute traumatic coagulopathy (ATC) is positively correlated with an increasing injury severity score (ISS), develops independent of prehospital fluid administration and subsequent hemodilution, and is associated with an increased risk of early death.[14,16] The presence of ATC may confound resuscitative efforts and increase mortality by exacerbating blood loss, increasing transfusion requirements, and prolonging hypoperfusion from sustained hypovolemic shock. Further, ATC can confound stabilization and treatment of traumatic brain injury and pulmonary contusions through potentiating intracranial hemorrhage and pulmonary edema, respectively. Currently, no prospective clinical studies are available in veterinary patients looking at the prevalence of an ATC.

Current Published Veterinary Literature

Most of the information regarding the prevalence of and therapeutic approach to ATC in veterinary medicine is derived from experimental animal models as well as extrapolated from human studies. One of the few prospective studies to evaluate hemostatic changes in spontaneously traumatized dogs[17] used an extensive hemostatic profile to evaluate 30 dogs presenting with blunt traumatic injuries. As compared to the healthy control group, traumatized dogs experienced a significant reduction in all measured hemostatic factors (coagulation factors, anticoagulant proteins, platelets, and plasminogen) as well as a significant prolongation in activated partial thromboplastin time (aPTT) and prothrombin time (PT) Similar to human studies, factor V depletion that was noted in approximately 76% of traumatized dogs. Soluble fibrin and fibrin degradation products (FDPs) were both significantly elevated in most traumatized dogs for which the former was used as an indicator of significant intravascular clotting and thrombin generation, while the latter was used as an indicator of fibrinolysis. Fibrinogen and the inhibitor α2-antiplasmin concentrations did not decrease significantly. Overall, their data provided evidence supporting the presence of an active coagulation process posttrauma; however, they provided no evidence surrounding the dynamic or time-sensitive nature or the relevance to injury severity posed by these changes in coagulation. Other limitations to their study involved the lack of standardization in reference to the time of blood sample collection, only collecting samples at one time point, and lack of evaluating D-dimers that is considered a more specific marker of active fibrinolysis as compared to FDPs. Considering the dynamic nature of coagulation posttrauma, these limitations make it challenging to develop a definitive conclusion or comparison between other study groups.

In 2011, abstract data were presented on the presence of coagulopathy in 41 posttrauma (blunt and penetrating) dogs.[a] This prospective study used both clinical and laboratory markers (lactate, platelet count, antithrombin, D-dimer, protein C, antiplasmin, plasminogen, and thromboelastography) to identify the incidence of coagulopathy. Overall outcome in dogs presenting with a coagulopathy was also evaluated. From their data, they reported that nonsurviving dogs and dogs suffering the most severe injuries were more hypocoagulable and that these trauma-associated coagulopathies were positively

correlated with the incidence of hemorrhage and transfusion requirements. The increased incidence of body cavity hemorrhage and need for blood transfusions was correlated with: decreasing platelet counts; decreasing markers of thromboelastography clot strength (maximum amplitude and *G*-value) and rate of clot formation (alpha angle); decreasing antithrombin and protein C concentrations; and increasing values of aPTT.

Etiology

It was once thought that the coagulopathy associated with trauma was primarily due to loss, dysfunction, or hemodilution of hemostatic factors and platelets. Loss was usually attributed to severe hemorrhage and consumption, hemodilution primarily from aggressive large-volume fluid resuscitation, and dysfunction from the inhibitory effects of concurrent metabolic acidosis and hypothermia on the activity of hemostatic serine proteases and platelets.[9] Over the past decade, current knowledge has instead revealed that this acute trauma/shock-related coagulopathy is a distinct, endogenous coagulopathy that can develop within as little as 30 minutes posttrauma.[7,18–20] It has been shown to develop before resuscitative efforts are initiated; independent from loss, consumption, or dilution of hemostatic factors or platelets; and prior to any influence from physiological factors such as metabolic acidosis and hypothermia.[12,21,22] This phenomenon has more recently been referred to as "ATC," "early coagulopathy of trauma," or "acute coagulopathy of trauma – shock."[12,21–23] For the remainder of this review, the authors will refer to trauma-associated coagulopathy as ATC. To date, controversy still surrounds the underlying mechanism of ATC. The 3 main hypotheses that currently account for ATC's manifestation of systemic hypocoagulation and hyperfibrinolysis include a disseminated intravascular coagulation (DIC) with a fibrinolytic phenotype,[10,24] an enhanced thrombomodulin-thrombin protein C pathway,[9,12,19,23–25] and a marked sympathoadrenal response leading to catecholamine-induced endothelial damage.[20,23,24]

ATC or DIC?

Parameters that have been reported by some investigators in the human literature to delineate ATC from DIC include: earlier onset of action; lack of microthrombi development; lack of association with clotting factor deficiency and induction of coagulopathy; and a sparing of platelet concentrations despite the presence of a marked coagulopathy.[9,21,22,24] Effects on fibrinogen concentrations have varied between studies with some reporting that fibrinogen concentrations are spared[9,12,18,26] while others displaying a significant decrease[24] in circulating fibrinogen. Similarly, evidence from human studies regarding coagulation factor consumption during the early stages of posttraumatic coagulopathy is also conflicting whereby significant coagulation factor consumption[27,28] as well as lack of factor consumption[9,12,20,23–25] have both been demonstrated in people during the early posttrauma period.

In an effort to resolve this controversy, studies have been conducted in attempts to identify the presence of DIC in the early posttraumatic period. However, 2 such observational studies in human trauma patients,[24,29] failed to demonstrate DIC in the early posttraumatic period. In these studies, the International Society of Thrombosis and Hemostasis (ISTH) DIC scoring system (see Figure 1) was implemented to identify patients with overt DIC. One of the studies even incorporated pathologic evidence of microthrombi in surgically excised and autopsied organs as a more confirmatory "gold standard" test for diagnosing DIC. Overall, the data from these studies did not support the occurrence of DIC up to 24 hours posttrauma. From the evidence presented thus far, it is evident that further well-powered, prospective randomized clinical trials are needed to fully elucidate whether ATC is a functional manifestation of DIC or some other coagulopathic mechanism. Unfortunately, the dynamic and time-sensitive nature of ATC[10,23,30] presents a significant challenge for achieving this goal. Comparing data collected by different investigators also poses a further challenge due the inherent heterogeneity that exits in the subsets of studied patients as well as the different methodological variations that have been used in the different investigation.[29]

The predominating hypotheses of ATC

Currently, there are 3 predominating hypotheses that attempt to explain the pathophysiological mechanism underlying ATC's clinical manifestation of systemic hypocoagulation with hyperfibrinolysis. One hypothesis contends that ATC is a phenotypic variation of classic DIC. Classically, DIC is described as initially being more prothrombotic and hypercoaguable in nature; a condition that then progresses into a consumptive, hypocoagulable, and hemorrhagic disorder if the primary underlying condition persists. However, some advocate that instead of initially experiencing DIC with a prothrombotic phenotype, that during the first 24–48 hours postinjury trauma patients suffer from DIC with a fibrinolytic phenotype.[10,23,31] Following the first 24–48 hours posttrauma the underlying coagulopathic nature then progresses to DIC with a thrombotic phenotype.[10,23,31] Immediately following trauma and shock, severe endothelial injury, hypoxia, and ischemia invokes marked

Risk Assessment: Does the patient have an underlying disorder (eg, sepsis, trauma, obstetric emergency) compatible with DIC?

Coagulation Assays:

a. Platelet count ($x10^9$/L)
   >100 = 0 points; > 50 to < 100 = 1 point; < 50 = 2 points

b. Elevated fibrin related markers (D-dimer or FDPs):
   No elevation = 0 points, moderate increase = 2 points, strong increase = 3 points

c. Fibrinogen (g/L)
   >1 = 0 points, < 1 = 1 point

d. Prolonged Prothrombin Time (PT) or International Normalization Ratio (INR)
   PT (in seconds): < 3 = 0 points, >3 < 6 = 1 point, >6 = 2 points
   INR: > 2.3 (two points), 1.4 to 2.3 (one point)

Overall Score:
Greater than or equal to 5 = compatible with overt DIC, repeat scoring daily

Less than 5 suggestive of non-overt DIC

Figure 1: International society of thrombosis and hemostasis DIC score.[24,29]

generation of thrombin with subsequent systemic fibrin formation. Concurrently, there is a massive release of tissue plasminogen activator into the circulation resulting in conversion of large amounts of plasminogen into plasmin. These 2 simultaneous events account for the proposed posttraumatic hyperfibrinolytic and hypocoaguable expression. This coagulopathic state is further described as developing from the effects of primary hyperfibrinogenolysis, secondary hyperfibrinolysis, and consumption of hemostatic factors and platelets. As the patient is resuscitated and circulatory perfusion restored then the later thrombotic state develops subsequent to greater expression of plasminogen activator inhibitor-1 as compared to tissue plasminogen activator.[31]

In contrast to DIC, that the second hypothesis contends that ATC is not initially a consumptive coagulopathy, but instead evolves from decreased thrombin degradation and increased thrombomodulin activity leading to enhanced activation of the thrombin-thrombomodulin protein C anticoagulant pathway.[9,12,25,30,32,33] In this hypothesis, the primary initiators of ATC are considered to be severe tissue injury and profound hypoperfusion. Even though thrombin is typically regarded as a prothrombotic agent via promoting fibrin formation, binding of thrombin to thrombomodulin switches it from its procoagulant function to its anticoagulant function via activation of protein C. Subsequently, activated protein C exerts anticoagulant properties via inhibition of factor Va and VIIIa while concurrently exerting fibrinolytic properties via suppressing plasminogen activator inhibitor-1activity and thrombin activatable fibrinolytic inhibitor formation. Again, the aforementioned events account for the phenotypic expression of ATC that is primarily characterized by systemic hypocoagulation and hyperfibrinolysis.

The final neurohormonal hypothesis[23] implicates the role of the posttraumatic sympathoadrenal response and subsequent catecholamine-induced endothelial damage as an integral component responsible for the phenotypic expression of ATC.[20,23,24] Trauma with tissue injury invokes a dose-dependent sympathoadrenal response and subsequent release of catecholamines into the circulation. Circulating catecholamines directly damage the endothelial glycocalyx in a dose-dependent fashion that, as a result, changes the endothelium from a more antithrombotic to a prothrombotic entity. This change in endothelial function allows for local hemostasis to take place at the site of injury. However, in order to prevent systemic coagulation and maintain local vascular perfusion, the body attempts to counterbalance the effects of the prothrombotic endothelium with an anticoagulable and fibrinolytic response in the fluid phase (whole blood).[23] The mechanism behind this counter-regulatory response is thought to involve the shedding of anticoagulant (heparin-sulfate and soluble thrombomodulin) and fibrinolytic (tissue-plasminogen activator) constituents from the damaged glycocalyx into the local circulation. However, the counter-regulatory response is considered a poorly adapted evolutionary mechanism.

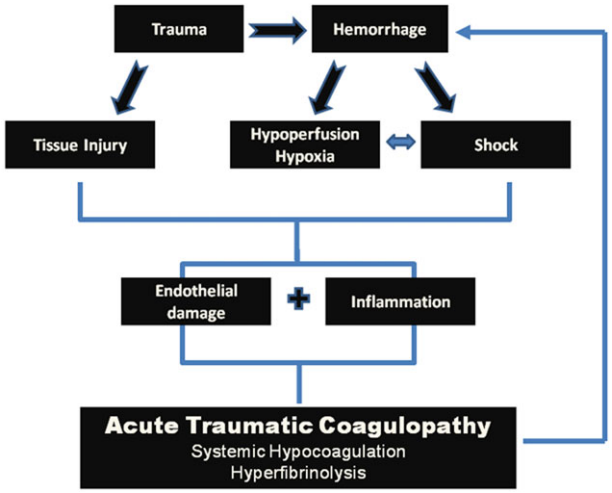

Figure 2: Initiators of acute traumatic coagulopathy.

As the degree of tissue trauma and endothelial damage increases, the counter-regulatory response rages out of control, resulting in both systemic hypocoagulation and hyperfibrinolysis.[20,24]

Initiators of acute traumatic coagulopathy

Six key factors have been shown to influence ATC (tissue injury, hypoperfusion, systemic inflammation, metabolic acidosis, hypothermia, and hemodilution); however, despite the diversity in proposed physiological mechanisms of ATC, only shock due to ongoing tissue hypoperfusion along with severity of tissue injury have been globally accepted as the 2 main initiators of ATC.[22,24,34] Considering not all patients with severe tissue injury or hypoperfusion develop ATC, other factors may contribute to its development. For example as discussed earlier, catecholamine-induced damage to the endothelial glycocalyx also contributes to increased protein C activation and hyperfibrinolysis.[20,22,24] Additionally, a less discussed contributor is the influence invoked from the known cross-talk between inflammation and coagulation. Complement proteins, in particular, are markedly increased immediately posttrauma and have been linked to increased expression of soluble thrombomodulin and enhanced activation of protein C.[23] Although, metabolic acidosis, hypothermia, and hemodilution may potentiate ATC, they are not considered the main initiating events. Rather, these influences serve to prolong the coagulopathic state and hinder therapeutic efforts. The exacerbation of ATC from acidosis, hypothermia, and hemodilution has been termed "trauma-induced coagulopathy" (see Figure 2).

Tissue injury and hypoperfusion

The severity of injury and degree of hypoperfusion has been shown to be positively correlated to the severity of coagulopathy that develops.[20,21,23] Interestingly, patients with severe tissue injury but suffering no other major physiological derangements (ie, hypoperfusion, acidosis, hypothermia) do not commonly present with ATC and generally suffer lower mortality;[34] therefore, tissue injury alone may not be enough to initiate ATC. The site and type of tissue injury may also play a role in the development of ATC. It is purported that traumatic injuries to the brain and long bones as well as the presence of a penetrating injury may be more commonly associated with the development of ATC. The combination of ATC and traumatic brain injury has been shown to correspond to a higher risk of mortality;[7,13,34] however, evidence is a somewhat conflicting regarding the actual role traumatic brain injury plays as an independent risk factor for ATC.[7]

Tissue and vascular injury exposes the subendothelial collagen to von Willebrand factor as well as exposes extravascular tissue factor to circulating activated factor VIIa resulting in the initiation of coagulation and subsequent thrombin formation. Thrombomodulin binds to thrombin and activates the protein C anticoagulant pathway that, via inhibition of plasminogen activator inhibitor-1, also promotes fibrinolysis. Vascular injury can further result in cleavage and dysfunction of thrombomodulin, antithrombin bound to endothelial heparin sulfate, tissue factor pathway inhibitor, and endothelial protein C receptor thereby disrupting the endothelial's anticoagulant mechanisms. In addition, endothelial injury results in the release of massive amounts of tissue plasminogen activator initially, and in conjunction with thrombin's ability to increase endothelial tissue plasminogen activator expression along with thrombin's indirect inhibition of plasminogen activator inhibitor-1 (via activated protein C) subsequent hyperfibrinolysis develops.

Hypoperfusion has been most commonly assessed by using base deficit concentrations as a reliable surrogate marker in human trauma patients;[35,36] however, hyperlactatemia and hypotension (systolic blood pressure < 90 mm Hg) have also been used. Hypoxia and ischemia subsequent to hypoperfusion exerts a dose-dependent effect on coagulation promoting a more anticoagulant and hyperfibrinolytic environment. In studies documenting coagulation factor deficiency, the more severe the hypoperfusion (as determined by declining base deficit [BD] values ≤ 13 mmol/L) the more significant reduction in serine protease activity and greater increase in transfusion requirements were observed.[27,28] Although, the exact mechanism of hypoperfusion-induced coagulopathy remains unclear it appears to be unrelated to the

degree of acidosis and presence of hypothermia. Hypoxia and ischemia without trauma has been shown to increase endothelial tissue plasminogen activator expression, upregulate endothelial adhesion molecules, induce de novo transcription of tissue factor from monocytes and vascular smooth muscle cells, as well as damage and subsequently activate the endothelium.[10] Furthermore, hypoperfusion delays the clearance of thrombin allowing a greater availability for thrombin to bind to thrombomodulin.[34] Increased thrombin-thrombomodulin binding results in enhanced protein C activation leading to systemic anticoagulation and hyperfibrinolysis.

Inflammation

Trauma or marked hemorrhage evoke an immediate and marked release of proinflammatory cytokines (tissue necrosis factor-α [TNF-α], interleukin [IL]-1, IL-6), anti-inflammatory cytokines (IL-4, IL-10, IL-13), chemokines (IL-8), alarmins (high mobility group box-1, heat shock proteins) as well as activation of the complement (C3a and C5a) pathways.[37,38] Although not fully elucidated, evidence supporting the cross-talk between inflammation and coagulation has been well documented over the past decade.[12,13,15,39–42] Proinflammatory cytokines, tissue factor, thrombin-thrombomodulin protein C pathway, endothelium, complement proteins, and platelets constitute the major players in this interplay between inflammation and coagulation.[12–15,39–42]

When describing the interplay between coagulation and inflammation during the posttraumatic period, the literature predominantly reviews the relationship between coagulation and inflammation as it pertains to the development of trauma-induced sepsis. However, this interplay typically involves a series of events that do not develop until 3–5 days posttrauma. Little to no data actually describe or evaluate the precise interaction between the two systems during the very acute period at which ATC occurs. As a result, the exact involvement of proinflammatory mediators contribute to the development of ATC remains poorly understood and somewhat conflicting. It is known that complement proteins play an integral role in regulating the innate immune response and their expression rises immediately posttrauma.[23] Further, it appears that the degree of complement activation correlates to the severity of tissue injury and hypoperfusion and has been shown to be associated with mortality.[13] In regards to ATC, complement activation upregulates thrombomodulin expression resulting in enhanced activation of protein C and platelet activation,[13,38] while the proinflammatory cytokines TNF-α, IL-1β, and IL-6 upregulate tissue factor expression on circulating monocytes and endothelial cells.[10,37,41,42] Overall the combined actions set the stage for enhanced thrombin-thrombodulin protein C activation with subsequent hypocoagulation and hyperfibrinolysis. During the later posttraumatic period (> 24 hours) inflammatory influences on coagulation favor a more prothrombotic tendency. Proinflammatory cytokines downregulate protein S,[13] endothelial-based heparin sulfate proteoglycans, thrombomodulin, and endothelial protein C receptor. Circulating concentrations of inactivated protein C and antithrombin decrease due to impaired production, consumptive losses, and/or degradation by elastase released from activated neutrophils.[42] In addition, impairment of activated protein C may also result from a relative protein S deficiency that develops as upregulated concentrations of complement C4 bind to over half of the circulating protein S.[42]

Metabolic acidosis and hypothermia

In the later stages of trauma and resuscitation, other physiological factors such as acidosis (pH < 7.2) and hypothermia (< 33–34°C) may exacerbate ATC.[9,12,13] The concurrent presence of coagulopathy, acidosis, and hypothermia is referred to as the "lethal triad" or "trauma triad of death" and is shown to confound ATC[43] by causing coagulation factor and platelet dysfunction as well as increased fibrinogen consumption and decreased platelet count.[26,44] It has been reported that the activity of the factor Xa/Va complex may be reduced by as much as 50% at a pH of 7.2, 70% at a pH of 7.0 and 90% at a pH of 6.8.[26] In a swine model,[44] induced states of metabolic acidosis (arterial pH ≤ 7.1) resulted in a hypocoagulable thromboelastography tracing as well as a significant decrease in fibrinogen concentrations and platelet counts. As compared to thromboelastography, traditional coagulation tests (APTT, PT, and activated clotting time) were not as sensitive for identifying the acidosis-induced hypocoagulable state. Of further interest was that infusion of bicarbonate to correct the arterial pH back to 7.4 failed to correct the state of hypocoagulation, therefore suggesting more than correction of pH is needed to reverse the adverse influence of acidosis–induced coagulopathy.

Similarly, accidental hypothermia below 33–34°C has been shown to decrease coagulation protease function activity and platelet aggregation.[9,13] It is not uncommon for casualties to present in a markedly hypothermic state due to environmental exposure, loss of intravascular volume, and poor perfusion that may be confounded later during aggressive fluid resuscitation with cool temperature fluids. However, it was observed in one review that less than 9% of human trauma patients present with a core temperature of

less than 35°C;[9] therefore, due to the acute nature of ATC, the influence of hypothermia may not be clinically significant.

Hemodilution

Marked decreases in intravascular pressure from massive blood loss causes a shift of extracellular water into the vascular space and subsequent dilution of hemostatic factors, red blood cells, and platelets. Traditional large-volume fluid resuscitation (ie, infusing 3 mLs of isotonic crystalloid for every 1 mL of shed blood)[7–9,12,15,21,22] during uncontrolled hemorrhage can actually exacerbate ATC. Large volume fluid resuscitation increases hydrostatic pressure; disrupts the formation of any preformed soft thrombi; dilutes hemostatic factors, platelets, and RBCs; reduces blood viscosity; disrupts the compensatory vasoconstrictive function of the blood vessels; and potentiates hypothermia and hyperchloremic metabolic acidosis (most noticeable with 0.9% saline infusion).[45,46] In addition, isotonic crystalloids and synthetic colloids provide no red blood cells, hemostatic factors, or platelets and, therefore, provide no direct effect on improving coagulation or oxygen carrying capacity. Furthermore, stored blood products can also contribute to hemodilution of coagulation factors (pRBCs) as well as platelets (pRBCs and stored plasma-based products). In addition, synthetic colloids are known to exert a dose-related coagulopathy and platelet dysfunction. This synthetic colloid-induced coagulopathy has been primarily associated with the hydroxyethyl starch solutions possessing a high-molecular weight and a greater degree of substitution (ie, hetastarch 600/0.75[b] and 670/0.75[c]), whereas the solutions with a lower molecular weight and lesser degree of substitution (ie, tetrastarch 130/0.4 [c,d]) are touted to be less coagulopathic.[47–49] Unfortunately, adequate data from well-designed prospective, randomized clinical trials to support this latter assumption are currently lacking in both human and veterinary medicine. In fact, more recent data suggest that all hydroxyethyl starch solutions impart some degree of adverse effect on coagulation.[50,51]

Diagnostic Evaluation of ATC

As mentioned earlier, data extracted from human studies indicate 10–25% of human trauma patients experience ATC that has been shown to prolong hemorrhage, deter resuscitative efforts, promote sepsis, and increase mortality by at least 4-fold. The fact that ATC is dynamic in nature and progresses acutely through various coagulopathic stages (ie, hypocoagulable, hyperfibrinolytic, hypercoagulable)[20,23,24] has presented a challenge for human physicians in being able to effectively and rapidly detect ATC. In addition, one must consider that each different phase of this dynamic coagulopathy may inherently require a different type of blood product component to successfully abate the ongoing coagulopathy.[20,23,24] To date, no validated test exists for reliably detecting or guiding treatment for ATC. This diagnostic deficiency has hindered the clinician's ability to provide timely, effective goal-directed therapy and curtail mortality. In order to counter the effects of ATC and increase survivability, it is imperative to be able to: (1) identify ATC at least within the first hour of presentation, and (2) institute immediate goal-directed therapy with appropriate blood component products to prevent any further ongoing hemorrhage.[46] In this context, appropriate goal-directed therapy specific to ATC should be able to target and correct relevant to deficiencies in. If ATC carries a 4-fold increase in the risk of death in veterinary trauma patients as it does in people, then it is equally paramount for veterinarians to have a rapid, reliable, and accurate method for identifying ATC early to improve survival.

Traditional tests of coagulation

One of the primary limitations for evaluating the presence of ATC is the lack of a readily available diagnostic test that is universally accepted, standardized, and precise; this is a limitation in human medicine, as well. In people, more commonly used traditional tests of coagulation such as the PT, aPTT, and the international normalized ratio (INR) along with measurement of fibrinogen concentration and platelet count has been used to identify the presence of ATC. Unfortunately, these tests do not adequately reflect the dynamic process of coagulation as they are measured at only one point in time. In addition, fibrinogen and platelet counts only provide absolute numerical values but do not reflect the functional activity of these entities. More commonly used values for defining ATC in human patients include a 50% prolongation of aPTT or PT, an INR $\geq$ 1.5, PT ratio (patient PT/mean laboratory PT) $>$ 1.5, or fibrinogen $<$ 1 g/L.[7,21,52–55] In a more recent retrospective cohort study of human trauma patients, a PT ratio $>$ 1.2 was shown to provide greater prediction of mortality and transfusion requirements and, thereby, was proposed as a better marker for defining ATC.[21] In veterinary patients, aPTT or PT values $>$ 1.5 times the mean of the laboratories reference interval has been commonly used as a cut-off for the presence of a significant coagulopathy.

Due to their static nature and ability to only evaluate plasma-borne mediators and states of hypocoagulability, aPTT and PT possess many inherent limitations for

identifying ATC. The aPTT and PT assays were mainly developed to assess bleeding disorders from factor deficiencies or those receiving oral anticoagulant therapy. They were never validated for evaluating ATC that some consider to develop unrelated to significant factor deficiency (ie, threshold below 30% of normal of any one factor). Also consider that prolongations in these assays may not even correlate reliably with the overall risk of bleeding.[56–59] In addition, as PT and aPTT are performed at a normal pH and at 37°C, they fail to account for physiological effects of hypothermia or metabolic acidemia; therefore, they may not be representative of the true in vivo coagulation status in a markedly hypothermic or acidemic trauma patient. Overall, the aforementioned limitations have accounted for the observations that aPTT and PT carry a poor predictive value for early detection of ATC.[9,12,60,61]

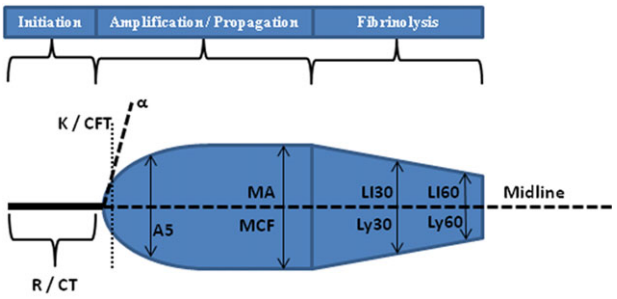

Figure 3: Composite of viscoelastic tests and phases of coagulation.[64,65] R, reaction time; CT, clotting time; K, kinetics; CFT, clot formation time; α, angle; MA, maximum amplitude; MCF, maximum clot firmness; LY or LI 30/60, lysis time at 30 minutes post-MA/MCF; A5, amplitude obtained at 5 minutes poststart of tracing.

Viscoelastic tests

With the paradigm of coagulation shifting from the traditional dual pathway cascade to a cell-based model,[62] viscoelastic tests (thromboelastography [TEG] and rotational thromboelastometry [ROTEM]) that evaluate clotting characteristics are considered more global tests of coagulation. Traditional coagulation tests (PT, aPTT, and INR) stop once fibrin formation starts (or the initiation phase of coagulation) and, therefore, are only sensitive at identifying hypocoagulation. On the other hand, viscoelastic tests are able to evaluate all components of the coagulation process allowing them to evaluate the entire coagulation process from fibrin formation to fibrinolysis;[63] therefore, these tests identify not only hypocoagulation, but also hypercoagulation and hyperfibrinolysis. Using electron microscopy, it was determined that the TEG reaction time and ROTEM clotting time correlated with the initiation phase of the cell-based model of coagulation; the TEG kinetics value and ROTEM clot formation time correlated with the amplification phase; and the TEG/ROTEM alpha angle correlated with the propagation phase or thrombin burst.[64] The TEG maximum amplitude or the ROTEM maximum clot firmness represent final clot formation; therefore, they provide an overall measure of maximum clot strength.[64] Figure 3 and Table 1 provide a comparison of the TEG and ROTEM parameters that are commonly evaluated.

The increasing use of viscoelastic tests both has provided a better understanding behind the physiological mechanism as well as the dynamic and time-sensitive nature of ATC. Implementation of viscoelastic tests in humans and animal models has shown ATC to be mainly a problem with clot strength that may account for the lack of sensitivity afforded by PT and aPTT.[27,31,64,66] Viscoelastic testing has further demonstrated that ATC is a dynamic and unpredictable entity progressing through normal coagulable, hypercoagulable, hypocoagulable, and a hyperfibrinolytic states.[23] The in vivo state of coagulation at any point in time, in part, may depend upon and reflect the severity of tissue injury. Data collected by Johansson et al revealed that patients with minor tissue injury (as measured by the ISS) display a predominantly normal viscoelastic tracing while patients suffering from moderate injury (ISS 10–25), severe injury (ISS 20–35), and massive tissue injury (ISS > 35) are increasingly more hypercoagulable, hypocoagulable, and hyperfibrinolytic, respectively.[64] Using rapid TEG (with tissue factor as an activator), Kashuk et al[19] identified primary hyperfibrinolysis in 34% of the most severely injured trauma patients; these patients were also most likely to require massive transfusions. Primary fibrinolysis was identified at a median time of 58 minutes posttrauma and its presence was significantly correlated to postinjury coagulopathy and hemorrhage-related deaths.[19] Conversely, patients requiring minimal blood transfusion therapy displayed predominantly a normal viscoelastic tracing.[19] In a hemorrhagic shock model utilizing pigs, White et al demonstrated that primary changes in hemostatic function began shortly after onset of traumatic hemorrhagic shock and were represented by decreasing concentrations of fibrinogen and reduction in overall clot strength as indicated by decreased maximum amplitude value measured via TEG. Interestingly, no significant changes in PT or aPTT were noted anytime during the experiment.[26] Other studies have observed similar results demonstrating a correlation between the measurement of clot strength via viscoelastic tests and the prevalence of ATC.[32,61,67] In light of these observations, a more functional definition of ATC has been proposed

Table 1: Comparison of parameters from thromboelastography and thromboelastometry.[64,65] R, reaction time; CT, clotting time; K, kinetics; CFT, clot formation time; α, angle; MA, maximum amplitude; MCF, maximum clot firmness; LY or LI 30/60, lysis time at 30 minutes post-MA/MCF; A5, amplitude obtained at 5 minutes poststart of tracing.

	Thromboelastography parameters	Thromboelastometry parameters
Clot time		
• Distance measured from the start of the tracing to point where each arm has diverged 1 mm from midline	Reaction time (R)	Clotting time (CT)
Clot kinetics (rate of clot formation)		
• Distance measured from the end of R or CT to the point at which the 2 arms of the tracing diverge by 20 mm	• Kinetics (k time)	• Clot formation time (CFT)
• Tangent of the curve between end of R and K/CFT	• α	• α
Clot strength or firmness		
• Maximal distance between 2 diverging arms of the tracing (reflects final clot formation)	• Maximal amplitude (MA)	• Maximal clot firmness (MCF)
• Measure of clot elasticity	• G or (5000∗MA)/(100-MA)	• Maximal clot elasticity (MCE)
• Amplitude obtained at "x" minutes poststart of tracing		• A "x" (A5 = amplitude at 5 minutes)
Clot lysis		
• Degree of amplitude reduction at 30 minutes post-MA/MCT	• LY30	• LI30 (% amplitude reduction)
• Degree of amplitude reduction at 60 minutes post-MA/MCT	• LY60	• LI60 (% amplitude reduction)

as a viscoelastic tracing displaying persistently reduced clot strength.[30,32,61]

Evident from the information already provided, it is not surprising that viscoelastic tests have been shown to be more predictive for not only detecting ATC but also in affording earlier identification of ATC as compared to traditional tests of coagulation.[32,61,68–71] In one prospective study[30] of human trauma patients, PT and PT ratio (calculated as the observed PT divided by the mean control PT) were only slightly prolonged in only approximately 30% of the most severely injured patients identified as having ATC. In the same study, ROTEM tracings consistently revealed an approximate 40% decrease (< 35 mm) in clot amplitude at 5 minutes poststart of tracing (A5) (see Figure 3) which the authors contended served as a reliable and clinically useful diagnostic marker of ATC. In the most severely injured patients, a clot amplitude of < 35 mm at A5 carried a detection rate of 60% for diagnosing ATC that was in comparison to a detection rate of only 33% for the point-of-care PT ratio of > 1.2. Interestingly, the ROTEM clotting time was not significantly prolonged in any patient. A more recent study[65] also demonstrated that the ROTEM A5 and A10 values were highly sensitive (eg, 0.96 and 1.00, respectively) for predicting a significant trauma-induced coagulopathy. Considering the acutely dynamic nature of ATC, any delay in diagnostic results may not be clinically useful as the patient's coagulation state in vivo may have already changed and the inappropriate transfusion product administered.

Different coagulopathic states require different transfusion products to successfully abate any ongoing coagulopathic hemorrhage. In nontraumatic human cardiac surgery and liver transplant patients the use of TEG and ROTEM has already been shown to reduce the need for inappropriate transfusions, decrease blood product requirements, and reduce the number of deaths, complications, and postoperative infections, therefore resulting in an overall increase in patient survival.[72] Recent evaluation of viscoelastic tests in human trauma patients have shown similar results in the ability of these tests to successfully guide-targeted transfusion requirements to include predicting patients requiring massive transfusions.[30,32,61] The one central advantage viscoelastic tests offer over traditional coagulation assays is the ability to detect hyperfibrinolysis that plays a central role in the phenotypic expression of ATC; therefore, these tests can accurately guide the appropriate institution of antifibrinolytics (eg, tranexamic acid and aminocaproic acid) that has been shown to reduce the risk of death from bleeding in certain subsets of trauma patients.[73,74]

Unfortunately, viscoelastic tests are not perfect. Although, they may differentiate between different coagulable states, they remain deficient in defining the absolute cause for those states. In addition, they remain in vitro tests; therefore, they fail to take into account influential effects provided by the endothelium and shear stress. Coagulation activators (eg, tissue factor, kaolin) used in viscoelastic tests leads to thrombin formation and, therefore, do not rely solely on the presence of

activated platelets to form thrombin that is required in vivo. In this regard, viscoelastic tests remain inadequate for detecting the inhibition that antithrombotic agents (eg, nonsteroidal anti-inflammatory drugs, GPIIb/IIIa receptor inhibitors) exert on platelet aggregation.[64] As compared to traditional assays of coagulation, the requirement for a higher degree of technical expertise, frequency of maintenance, and quality assurance also limits the wide-spread use of viscoelastic tests.[66] Some evidence has even shown that viscoelastic tests may be no more sensitive and even less specific for identifying a critical deficiency in coagulation factor activity (defined as a circulating concentration of less than 30% of normal) in human trauma patients as compared to traditional coagulation assays.[27]

Predictive scoring systems

Incorporating predictive scoring systems for individual risk stratification in trauma patients that present with bleeding and coagulopathy has also been presented as another approach for achieving early diagnosis of ATC and identification of human patients requiring massive transfusions.[14,75] One such predictive scoring system is the trauma associated severe hemorrhage (TASH) score, which incorporates several physiological and injury-related variables (eg, hemoglobin, base excess, systolic blood pressure, heart rate, gender, injury pattern) to assess the persistence of bleeding by using the probability of massive transfusion as a surrogate index. Implementation could facilitate early identification of ATC, allow for rapid therapeutic intervention, and potentially decrease mortality. Other predictive scoring systems have also been evaluated and found to have relative equivalent value in predicting the need for massive transfusions as compared to the TASH.[75] To the authors' knowledge no such scoring system exists in veterinary medicine, but future development and institution of a predictive scoring system may help guide diagnosis, therapy, and improve overall survivability.

How do you diagnose ATC in your veterinary patient?

Unfortunately, no one standard validated assay or prediction index is available in human or veterinary medicine for reliably or accurately identifying ATC. Viscoelastic tests (i.e. TEG and ROTEM) appear to be more sensitive for detecting ATC early;[77] however, most veterinary clinics do not currently have readily available access to these tests. This makes the diagnosis or identification of the presence of ATC in our veterinary patients challenging. It may simply be based off clinical judgment and intuitions, by taking into account the patient's history, presenting condition, and initial laboratory data (eg, BD, lactate, blood pressure, aPTT/PT). Extracting evidence from available human literature, it seems reasonable that the following would be highly suggestive of the presence of ATC:

- History of sustaining severe trauma with marked tissue injury (penetrating or blunt) and presence of marked hypoperfusion (eg, systolic blood pressure < 80 mm Hg or MAP < 60 mm Hg; BD < − 6 mmoL; lactate > 5 mmol/L[76,e]).
- Presence of hemorrhagic shock, uncontrollable intracavitary hemorrhage, or spontaneous bleeding from wounds, catheters sites.
- Viscoelastic tracing (TEG/ROTEM) displaying a persistently decreased clot strength of <40% of mean reference value, or prolonged traditional coagulation assays (aPTT/PT) of > 1.5 times the laboratory mean.

Summary

Acute traumatic coagulopathy is a distinct, endogenous hypocoagulopathic state found to be present in 10–25% of severely injured human patients upon hospital admission. It develops both early in the posttraumatic period (≤ 1 hour) and independently from the effects of hemodilution, acidosis, or hypothermia. Investigations into the prevalence and etiology of ATC has expounded over the past few years; however, controversy and conflicting data still surround the exact underlying pathophysiology (DIC versus enhanced activated protein C pathway). From the current evidence it is obvious that ATC is both dynamic and multifactorial in nature. Increasing severity of tissue injury in conjunction with systemic hypoperfusion appears to be the 2 main initiators of ATC; however, neurohormonal activation, systemic inflammation, and widespread endothelial damage may similarly have an important influential role. Hemodilution, metabolic acidosis, and hypothermia only serve to potentiate ATC and further hinder resuscitative efforts; they are not considered initiators of ATC. The exacerbation of ATC due to the combined effects of acidosis, hypothermia, and hemodilution has been termed by some as "trauma-induced coagulopathy" to delineate the between the two mechanistically different coagulopathic entities. Gaining a better understanding behind the pathophysiology of ATC will undoubtedly improve diagnosis and management of trauma patients.

Due to its dynamic nature, ATC is challenging to diagnose. The fact that ATC hinders resuscitative efforts and significantly increases the risk of mortality mandates a method to reliably and immediately detect its presence as well as guide targeted transfusion strategies. Viscoelastic tests currently hold the most promise for providing the clinician this viable information; however, as new data evolves a more comprehensive stratification process

may prove to be even more advantageous. Currently, evidence describing the prevalence of ATC in veterinary patients is sparse, forcing the clinician to extrapolate information from human studies and experimental animal models.

Footnotes

[a] Holowaychuk M, Hanel R, O'Keefe K, et al. Prognostic value of coagulation parameters in dogs following trauma. In: Proceedings of the International Veterinary Emergency and Critical Care Symposium; 2011: Nashville, USA. p. 729.
[b] Hespan, B. Braun Medical Inc., Bethlehem, PA.
[c] Hextend, Hospira Inc., Lake Forest, IL.
[d] Voluven, Hospira Inc.
[e] Boysen S. Lactate and the critically ill patient. In: Proceedings of the Proceedings of the International Veterinary Emergency and Critical Care Symposium; 2006: San Antonio, USA.

References

1. Ertmer C, Kampmeier T, Rehberg S, et al. Fluid resuscitation in multiple trauma patients. Curr Opin Anaesthesiol 2011; 24:202–208.
2. Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. J Trauma 2006; 60(6 Suppl):S3–S11.
3. Lenz A, Franklin GA, Cheadle WG. Systemic inflammation after trauma. Injury 2007; 38:1336–1345.
4. Muir W. Trauma: physiology, pathophysiology, and clinical implications. J Vet Emerg Crit Care 2006; 16:253–263.
5. McGwin G Jr, Nunn AM, Mann JC, et al. Reassessment of the trimodal mortality distribution in the presence of a regional trauma system. J Trauma 2009; 66:526–530.
6. Heckbert SR, Vedder NB, Hoffman W, et al. Outcome after hemorrhagic shock in trauma patients. J Trauma 1998; 45:545–549.
7. Engels PT, Rezende-Neto JB, Al Mahroos M, et al. The natural history of trauma-related coagulopathy: implications for treatment. J Trauma 2011; 71(5 Suppl 1):S448–S455.
8. Spinella PC, Holcomb JB. Resuscitation and transfusion principles for traumatic hemorrhagic shock. Blood Rev 2009; 23:231–240.
9. Frith D, Brohi K. The acute coagulopathy of trauma shock: clinical relevance. Surgeon 2010; 8:159–163.
10. Gando S, Sawamura A, Hayakawa M. Trauma, shock, and disseminated intravascular coagulation: lessons from the classical literature. Ann Surg 2011; 254:10–19.
11. Cohen MJ, Call M, Nelson M, et al. Critical role of activated protein C in early coagulopathy and later organ failure, infection and death in trauma patients. Ann Surg 2012; 255:379–385.
12. Brohi K. Trauma induced coagulopathy. JR Army Med Corps 2009; 155:320–322.
13. Ganter MT, Pittet JF. New insights into acute coagulopathy in trauma patients. Best Pract Res Clin Anaesthesiol 2010; 24:15–25.
14. Maegele M, Lefering R, Yucel N, et al. Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. Injury 2007; 38:298–304.
15. Midwinter MJ, Woolley T. Resuscitation and coagulation in the severely injured trauma patients. Phil Trans R Soc B 2011; 366:192–203.
16. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma 2003; 54:1127–1130.
17. Mischke R. Acute haemostatic changes in accidentally traumatised dogs. Vet J 2005; 169:60–64.
18. Brohi K, Cohen MJ, Ganter MT, et al. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? Ann Surg 2007; 245:812–818.
19. Kashuk JL, Moore EE, Sawyer M, et al. Primary fibrinolysis is integral in the pathogenesis of the acute coagulopathy of trauma. Ann Surg 2010; 252:434–442.
20. Ostrowski SR, Sørensen AM, Larsen CF, et al. Thrombelastography and biomarker profiles in acute coagulopathy of trauma: a prospective study. Scand J Trauma Resusc Emerg Med 2011; 19:64.
21. Frith D, Goslings JC, Gaarder C, et al. Definition and drivers of acute traumatic coagulopathy: clinical and experimental investigations. J Thromb Haemost 2010; 8:1919–1925.
22. Wafaisade A, Wutzler S, Lefering R, et al. Drivers of acute coagulopathy after severe trauma: a multivariate analysis of 1987 patients. Emerg Med J 2010; 27:934–939.
23. Johansson PI, Ostrowski SR. Acute coagulopathy of trauma: balancing progressive catecholamine induced endothelial activation and damage by fluid phase anticoagulation. Med Hypotheses 2010; 75:564–567.
24. Johansson PI, Sørensen AM, Perner A, et al. Disseminated intravascular coagulation or acute coagulopathy of trauma shock early after trauma? An observational study. Crit Care 2011; 15:R272.
25. Bouillon B, Brohi K, Hess JR, et al. Educational initiative on critical bleeding in trauma: Chicago, July 11–13, 2008. J Trauma 2010; 68:225–230.
26. White NJ, Martin EJ, Brophy DF, et al. Coagulopathy and traumatic shock: characterizing hemostatic function during the critical period prior to fluid resuscitation. Resuscitation 2010; 81:111–116.
27. Rizoli SB, Scarpelini S, Callum J, et al. Clotting factor deficiency in early trauma-associated coagulopathy. J Trauma 2011; 71(5 Suppl 1):S427–S434.
28. Jansen JO, Scarpelini S, Pinto R, et al. Hypoperfusion in severely injured trauma patients is associated with reduced coagulation factor activity. J Trauma 2011;71(5 Suppl 1):S435–S440.
29. Rizoli S, Nascimento B Jr, Key N, et al. Disseminated intravascular coagulopathy in the first 24 hours after trauma: the association between ISTH score and anatomopathologic evidence. J Trauma 2011; 71(5 Suppl 1):S441–S447.
30. Davenport R, Manson J, De'Ath H, et al. Functional definition and characterization of acute traumatic coagulopathy. Crit Care Med 2011; 39:2652–2658.
31. Gando S. Acute coagulopathy of trauma shock and coagulopathy of trauma: a rebuttal. You are now going down the wrong path. J Trauma 2009; 67:381–383.
32. Brohi K, Cohen MJ, Davenport RA. Acute coagulopathy of trauma: mechanism, identification and effect. Curr Opin Crit Care 2007; 13:680–685.
33. Brohi K, Cohen MJ, Ganter MT, et al. Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. J Trauma 2008; 64:1211–1217.
34. Hess JR, Brohi K, Dutton RP, et al. The coagulopathy of trauma: a review of mechanisms. J Trauma 2008; 65:748–754.
35. Mofidi M, Hasani A, Kianmehr N. Determining the accuracy of base deficit in diagnosis of intra-abdominal injury in patients with blunt abdominal trauma. Am J Emerg Med 2010; 28:933–936.
36. Davis JW, Parks SN, Kaups KL, et al. Admission base deficit predicts transfusion requirements and risk of complications. J Trauma 1996; 41:769–774.
37. Schouten M, Wiersinga WJ, Levi M, et al. Inflammation, endothelium, and coagulation in sepsis. J Leukoc Biol 2008; 83:536–545.
38. Lenz A, Franklin GA, Cheadle WG. Systemic inflammation after trauma. Injury 2007; 38:1336–1345.
39. van der Poll T, Boer JD, Levi M. The effect of inflammation on coagulation and vice versa. Curr Opin Infect Dis 2011; 24:273–278.
40. Strukova S. Blood coagulation-dependent inflammation. Coagulation-dependent inflammation and inflammation-dependent thrombosis. Front Biosci 2006; 11:59–80.
41. Ioannou A, Lucca JD, Tsokos GC. Immunopathogenesis of ischemia/reperfusion-associated tissue damage. Clin Immunol 2011;141:3–14.
42. Levi M, van der Poll T. Inflammation and coagulation. Crit Care Med 2010; 38:S26–S34.
43. Kauvar DS. Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. J Trauma 2006; 60:S3–S11.
44. Darlington DN, Kheirabadi BS, Delgado AV, et al. Coagulation changes to systemic acidosis and bicarbonate correction in swine. J Trauma 2011; 71:1271–1277.

45. Lu YQ, Cai XJ, Gu LH, et al. Experimental study of controlled fluid resuscitation in the treatment of severe and uncontrolled hemorrhagic shock. J Trauma 2007; 63:798–804.
46. Durusu M, Eryilmaz M, Oztürk G, et al. Comparison of permissive hypotensive resuscitation, low-volume fluid resuscitation, and aggressive fluid resuscitation therapy approaches in an experimental uncontrolled hemorrhagic shock model. Ulus Travma Acil Cerrahi Derg 2010; 16:191–197.
47. Todd SR, Malinoski D, Schreiber M. Hextend attenuates the hypercoagulability following severe liver injury in swine. J Trauma 2004; 56:226.
48. Dailey SE, Dysart CB, Langan DR, et al. An in vitro study comparing the effects of Hextend, Hespan, normal saline, and lactated ringer's solution on thrombelastography and the activated partial thromboplastin time. J Cardiothorac Vasc Anesth 2005; 19:358–361.
49. Roche AM, Mythen MG, James MF. Effects of a new modified balanced hydroxyethyl starch preparation (Hextend) on measures of coagulation. Br J Anaesth 2004; 92:154–155.
50. Hartog CS, Bauer M, Reinhart K. The efficacy and safety of colloid resuscitation in the critically ill. Anesth Analg 2011; 112:156–164.
51. Hartog CS, Kohl M, Reinhart K. A systematic review of third-generation hydroxyethyl starch (HES 130/0.4) in resuscitation: safety not adequately addressed. Anesth Analg 2011; 112:635–645.
52. Hess JR, Lindell AL, Stansbury LG, et al. The prevalence of abnormal results of conventional coagulation tests on admission to a trauma center. Transfusion 2009; 49:34–39.
53. Brohi K, Singh J, Heron M, et al. Acute traumatic coagulopathy. J Trauma 2003; 54:1127–1130.
54. Yuan S, Ferrell C, Chandler WL. Comparing the prothrombin time INR versus the APTT to evaluate the coagulopathy of acute trauma. Thromb Res 2007; 120:29–37.
55. Maegele M, Paffrath T, Bouillon B: Acute traumatic coagulopathy in severe injury—incidence, risk stratification, and treatment options. Dtsch Arztebl Int 2011; 108:827–835.
56. Segal JB, Dzik W. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: and evidence based review. Transfusion 2005; 45:1413–1425.
57. Holland L, Sarode R. Should plasma be transfused prophylactically before invasive procedures? Curr Opin Hematol 2006; 13:447–451.
58. Chang WJ, Sum C, Kuperan P. Causes of isolated prolonged activated partial thromboplastin time in an acute care general hospital. Singapore Med J 2005; 46:450–456.
59. Kozak EA, Brath LK. Do "screening" coagulation tests predict bleeding in patients undergoing fiberoptic bronchoscopy with biopsy? Chest 1994; 106:703–705.
60. Ganter MT, Pittet JF. New insights into acute coagulopathy in trauma patients. Best Pract Res Clin Anaesthesiol 2010; 24:15–25.
61. Cotton BA, Faz G, Hatch QM, et al. Rapid thrombelastography delivers real-time results that predict transfusion within 1 hour of admission. J Trauma 2011; 71:407–414.
62. Smith SA. The cell-based model of coagulation. J Vet Emerg Crit Care 2009; 19:3–10.
63. Ganter MT, Hofer CK. Coagulation monitoring: current techniques and clinical use of viscoelastic point-of-care coagulation devices. Anesth Analg 2008; 106:1366–1375.
64. Johansson PI. Coagulation monitoring of the bleeding traumatized patient. Curr Opin Anesthesiol 2012; 25: 235–241.
65. Woolley T, Midwinter M, Spencer P, Watts S, Doran C, Kirkman E. Utility of interim ROTEM(®) values of clot strength, A5 and A10, in predicting final assessment of coagulation status in severely injured battle patients. Injury. 2012; Epub ahead of print. Available at: http://www.sciencedirect.com/science/article/pii/S0020138312001076. Accessed September 17, 2012.
66. Davenport R, Khan S. Management of major trauma hemorrhage: treatment priorities and controversies. Br J Haemotol 2011; 155:537–548.
67. Jeger V, Zimmermann H, Exadaktylos AK. The role of thrombelastography in multiple trauma. Emerg Med Int 2011; 2011:895674.
68. Gonzalez E, Pieracci FM, Moore EE, et al. Coagulation abnormalities in the trauma patient: the role of point-of-care thromboelastography. Semin Thromb Hemost 2010; 36:723–737.
69. Geeraedts LM Jr, Kaasjager HA, van Vugt AB, et al. Exsanguination in trauma: a review of diagnostics and treatment options. Injury 2009; 40:11–20.
70. Kashuk JL, Moore EE, Sawyer M, et al. Postinjury coagulopathy management: goal directed resuscitation via POC thrombelastography. Ann Surg 2010; 251:604–614.
71. Doran CM, Woolley T, Midwinter MJ. Feasibility of using rotational thromboelastometry to assess coagulation status of combat casualties in a deployed setting. J Trauma 2010; 69(Suppl 1):S40–S48.
72. Craig J, Aguiar-Ibanez R, Bhattacharya S, et al. Health Technology Assessment Report 11: the clinical and cost effectiveness of thromboelastography/thromboelastometry. 2008. Available at: http://www.healthcareimprovementscotland.org/previous_resources/hta_report/hta/hta_11.aspx. Accessed January 18, 2012.
73. Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 2010; 376:23–32.
74. Roberts I, Shakur H, Afolabi A, et al; CRASH-2 collaborators. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet 2011; 377:1096–1101.
75. Nunez TC, Voskresensky IV, Dossett LA, et al. Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? J Trauma 2009; 66:346–352.
76. Pang DS, Boysen S. Lactate in veterinary critical care: pathophysiology and management. J Am Anim Hosp Assoc 2007;43: 270–279.