

Goldilocks and Trauma Patients: When Is Hemostasis “Just Right”?

Christine S. Rinder, MD

*Departments of Anesthesiology and Laboratory Medicine
Fitkin 617*

Yale University School of Medicine

333 Cedar Street

New Haven, CT 06520-8035 USA

christine.rinder@yale.edu

Learning Objectives: On completion of this article, the reader should be able to 1) appreciate the potential of the trauma patient to develop bleeding from either a life-threatening coagulopathy or a depletion of coagulation factors caused by disseminated intravascular coagulation; 2) understand the ways that, in the trauma patient, hypothermia and acidosis create a coagulopathy that may be refractory to transfusion therapy; 3) recognize the potential for recombinant factor VIIa to aid in the treatment of hemorrhagic trauma patients, and understand that acidosis and thrombocytopenia may limit the drug's efficacy; and 4) appreciate that imbalance of four endogenous systems—the proinflammatory cascade, the procoagulant pathway, endogenous anticoagulants, and fibrinolysis—all contribute to the development of disseminated intravascular coagulation in the trauma patient.

Abstract

Trauma patients can present a uniquely challenging hemostatic picture, one that is dominated, especially early on, by a bleeding coagulopathy that appears refractory to transfusion therapy. The importance of hypothermia and acidosis, in particular, to the development of this coagulopathy is increasingly appreciated, as is the inability of transfused blood components to achieve hemostasis in cold, acidotic tissues. By contrast, the development of disseminated intravascular coagulation (DIC) in the trauma patient is a consequence of imbalance in the activation of procoagulant, inflammatory, anticoagulant, and fibrinolytic systems. This DIC state develops when toxic levels of cytokines such as TNF- α , IL-1 β , and IL-6 and systemic activation of procoagulant pathways culminate in widespread fibrin deposition in the microvasculature. The combined proinflammatory and procoagulant activity is on so massive a scale that endogenous anticoagulants such as antithrombin III, tissue factor pathway inhibitor, and activated protein C are overwhelmed, and efforts to keep the fibrin-occluded microvasculature patent by activity of the fibrinolytic system are frustrated by elevated and sustained production of the endogenous plasmin antagonist, plasminogen activator inhibitor-1. The dysfunctional activity of these processes that are normally so carefully orchestrated may culminate in a vasculopathy, leading to multiorgan failure and bleeding resulting from consumptive depletion of coagulation factors. This article reviews advances in the understanding of this complex pathophysiology, along with recent findings that may guide its treatment.

Coagulation management for the trauma patient seems a conundrum from the outset. Major trauma may be associated with a coagulopathy that can directly cause life-threatening bleeding. Alternatively, trauma can result in a state of disseminated intravascular coagulation (DIC), in which microvascular thrombosis produces multiple organ dysfunction, depletes coagulation factors, and eventually leads to bleeding. These two entities, a profound bleeding diathesis and indiscriminate fibrin clot formation, appear to occupy opposite ends of the coagulation spectrum, yet the trauma patient is at risk for both. What clinical features predispose to either of these states? Do they have distinct temporal profiles? This review will examine the basic pathophysiology underlying each of these coagulation abnormalities, with specific attention to those models relevant to trauma patients.

Bleeding Caused by Trauma Coagulopathy

For the patient with multiple trauma, the development of a coagulopathy is a major and all too common contributor to poor outcome. Hemodilution may be a factor when more than one blood volume (10 to 12 units of red cells) has been given, but studies have shown a poor correlation between the amount of blood products given and presence of coagulation defects.^{1,2} Cosgriff et al³ demonstrated that 47% of patients with trauma requiring ≥ 10 units of packed red blood cells over the first 24 hours developed a bleeding disorder that was unrelated to levels of hemostatic factors. Acidemia, hypothermia, severity of injury, and hypotension were all identified as risk factors predisposing to a bleeding diathesis.³ Indeed, acidemia and hypothermia, in particular, have such a strong association with coagulopathy⁴ and are such inevitable components of lengthy, aggressive operative procedures, that over the last decade, immediate priorities for the patient with multiple trauma have undergone a dramatic change. Instead of immediate operative correction of *all* injuries in what was once thought of as “the golden period,” trauma surgeons are now focusing their earliest efforts largely on operations aimed at controlling hemorrhage and clearing contaminated fields, so-called “damage control surgery.”⁵ By delaying all but the most critical procedures, trauma complications such as hypovolemia, acidosis, and hypothermia may be corrected prior to challenging the patient with definitive, often lengthy, surgical repairs.

Pathophysiology of the Bleeding Coagulopathy Associated with Hypothermia and Acidemia. Acidemia and hypothermia are so frequently associated with a coagulopathy in the trauma patient that they are known as “the vicious triad.”⁶ Trauma-associated hypothermia carries a higher mortality than either trauma or hypothermia occurring alone.^{6,7} The cause of the bleeding diathesis associated with hypothermia is multifactorial and is thought to include dysfunction of soluble coagulation and impairment of platelet and endothelial cell function. Hypothermia is known to slow enzymatic reactions; as a general rule, for every 10°C decrease in temperature, enzyme activity is reduced by approximately 50%.⁸ Accordingly, it is no surprise that soluble coagulation, a cascade of enzymatic reactions, is adversely affected by hypothermia. It has even been suggested that standard prothrombin time (PT-INR) and activated partial thromboplastin time (aPTT) assays for measuring coagulation should be performed at the actual core temperature of the patient to assess the true coagulation status of the patient.³ This maneuver might bring these assays marginally closer to depicting in vivo coagulation; however, these acellular assays are, at best, only crude simulations of physiologic coagulation as it actually occurs in the trauma patient. During in vivo hemostasis, cell surfaces are major (and often pivotal) factors in determining whether a clot will successfully arrest bleeding. Accordingly, the goal of giving an

Dr. Rinder has no conflicts of interest to disclose.

accurate representation of in vivo clotting cannot be achieved by the routine PT-INR and aPTT coagulation tests, even with temperature correction.

Wolberg et al⁸ recently used *cell-based* clotting assays and specific platelet function tests to determine the degree to which hypothermia, in the range common to trauma patients, affects these critical aspects of coagulation. They found that for temperatures in the range of 33 to 36°C, membrane-associated coagulation enzyme activities were only minimally reduced compared with their kinetics at 37°C. By contrast, platelet adhesion and aggregation were significantly reduced at 33°C compared with 37°C, suggesting that modest hypothermia may predominantly impair platelet-based hemostasis in the arterial circulation. For more severe hypothermia, that is, temperatures below 33°C, both platelet function and coagulation enzyme activity were impaired, likely contributing to coagulopathy under these conditions. However, fibrinolysis in trauma patients does not appear to be affected by hypothermia, at least at temperatures between 33 and 37°C.⁹

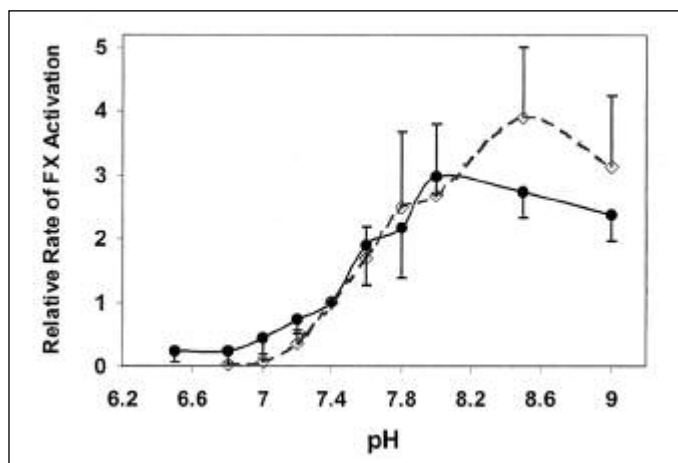


Figure 1. Effect of decreasing pH of the reactions of the rate of FXa formation by the FVIIa/TF complex (closed circles) and the rate of FXa formation by FVIIa alone on phospholipids vesicles (open diamonds). The rates of reactions have all been set to 1 at a pH of 7.4 for comparison. Reprinted with permission from Meng et al.¹⁰

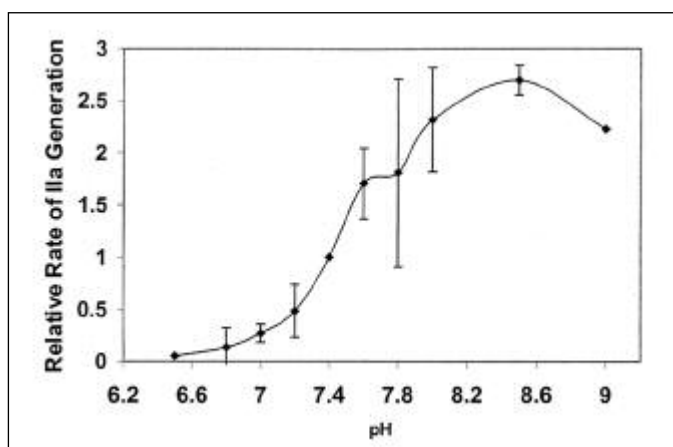


Figure 2. Effect of decreasing the pH of the reactions on the rate of prothrombin activation by the FXa/FVa complex on phospholipids vesicles. The rates of the reactions have all been set to 1 at a pH of 7.4 for comparison. Reproduced with permission from Meng et al.¹⁰

Acidosis has a particularly detrimental effect on coagulation. A recent study by Meng et al¹⁰ demonstrated that the rate of factor Xa (FXa) generation by the factor VIIa (FVIIa)/tissue factor complex was reduced by 55% at a pH of 7.0 compared with 7.4. Even more notably, the activity of the FXa/FVa prothrombinase complex was decreased by 70% at pH 7.0 (Figs. 1 and 2). These findings are in accord with the in vivo studies of Cosgriff et al,³ who found that admission pH <7.1 was highly predictive of the development of a bleeding coagulopathy, and with the finding of Kaplan and Kellum¹¹ that initial base deficit predicts outcome from major vascular injury.

Acidosis, like hypothermia, also adversely affects platelet function, particularly activation and aggregation, to physiologic agonists such as low-dose thrombin, ADP, and epinephrine. One mechanism responsible for this loss of function is the ability of high concentrations of extracellular H⁺ ions to impair the activity of the platelet membrane Na⁺/H⁺ antiporter.¹² One of the earliest events in platelet activation is alkalization of the platelet cytosol by this antiporter, a step critical to the subsequent transmembrane calcium influx,¹³ phosphoinositide cycle regulation,¹⁴ and binding of fibrinogen to its platelet surface receptor, glycoprotein IIb/IIIa.¹⁵ At pH ≤7.0, the Na⁺/H⁺ antiporter is unable to achieve the intracytosolic alkalization¹⁶ needed for these operations to take place, and platelet granule release, as well as aggregation, are inhibited.¹⁷ This effect is very rapid,¹³ suggesting that it is the extracellular pH and/or the intracellular-extracellular transmembrane pH gradient that is critical to the opening of these antiporter channels. When platelets enter the microcirculation of acidotic tissue, their ability to respond to local stimuli may become rapidly impaired. Although the effects of acidosis on platelets are reversible,¹⁸ the minimum time required for restoration of platelet function is unknown. In addition, the systemic pH may underestimate the local pH (and associated platelet inhibition) present in low-flow regions of the massively traumatized patient. Animal models of severe blood loss and shock suggest that acidosis in tissue beds, such as skeletal muscle, may persist long after resuscitation and seeming correction of the systemic acidosis.¹⁹ Thus, platelets may become functionally inhibited following passage through severely acidotic tissues despite a corrected systemic pH.

In summary, the bleeding coagulopathy associated with trauma is largely generated by factors extrinsic to the hemostatic system, that is, acidosis and hypothermia, rather than an insufficiency of hemostatic elements or an abundance of clot inhibitors and destabilizers. Accordingly, platelets and clotting factors that are transfused are unlikely to be any more successful than endogenous hemostatic components until these systemic abnormalities are corrected. Unfortunately, there is no clear evidence for an optimum resuscitation fluid from a hemostatic perspective; both hypertonic saline and colloids like hetastarch (in large amounts) have the potential to directly and adversely affect coagulation.²⁰⁻²² Alternatively, if large volumes of crystalloid are used in an actively bleeding patient, clotting studies such as the PT-INR and aPTT become prolonged from a dilutional coagulopathy. Temporary correction of the patient's pH by administration of sodium bicarbonate is not clearly efficacious in decreasing bleeding attributable to acidosis until resuscitation is achieved, and may also have its own anticoagulant effects.²³

Specific Testing

Basic coagulation tests (platelet count, PT-INR, aPTT, and fibrinogen level) need to be readily available and monitored frequently for optimum management of the patient with multiple trauma.²⁴ Thrombocytopenia is a major source of microvascular bleeding, and platelet counts need to be maintained at 50,000/μL or greater.¹ The PT-

INR is a measure of the tissue factor VII pathway, and when elevated in isolation generally reflects a deficiency of factor VII. As a rule, INR elevations are not associated with risk of generalized bleeding unless the INR is over 1.8 and associated with an elevated aPTT.² The aPTT is affected by multiple enzymatic reactions, and prolongation of the aPTT by more than 1.8 times the control value has been associated with significant bleeding.²⁴ Fibrinogen is an essential building block for optimum soluble coagulation and platelet function as well. Fibrinogen levels ≤ 80 mg/dL will cause prolongation of both the PT-INR and aPTT, and bleeding becomes excessive when fibrinogen levels drop below 50 mg/dL.

Point-of-care tests like thromboelastography (TEG) may be useful adjuncts to the more traditional coagulation tests in the management of the bleeding trauma patient.^{25,26} The TEG examines whole blood thrombus formation and lysis, measuring the force generated by the developing clot against a pin inside an oscillating container. The measured force is converted into a tracing whose shape gives insight into the number and function of platelets, the activity of soluble coagulation factors, and the activity of endogenous fibrinolytic enzymes. The test requires at least 40 minutes for a complete assessment of these parameters, and in institutions with good clinical laboratory back-up, TEG testing may not be appreciably faster than measurement of the more traditional platelet count, PT-INR, aPTT, and fibrinogen. However, when rapid turnaround of laboratory tests is not available, the TEG may provide timely insight into the coagulation status of the trauma patient.

Novel Therapeutic Options

Recombinant activated human coagulation factor VII (rFVIIa; NovoSeven, Novo Nordisk Pharmaceuticals, Inc., Princeton, NJ) was developed to treat bleeding in hemophilic patients with inhibitory antibodies to transfused FVIII.²⁷ The rFVIIa binds to tissue factor at the site of vascular injury, thereby potentiating thrombin formation and, ultimately, formation of a fibrin clot. The fact that rVIIa requires tissue factor for its activity gives it a site-specificity not shared by other activated factor concentrates, theoretically decreasing the risk of unintended clot formation in healthy blood vessels. In hemophilic patients, rFVIIa has proven to be remarkably effective and safe, stimulating interest in its use in nonhemophilic patients.

In trauma patients, rVIIa has been given on a compassionate-use basis, and case reports have attested to its efficacy in treatment of the patient with coagulopathic trauma.²⁸ A recent report describing its use in 81 patients with coagulopathic trauma who were treated at the Shock Trauma Center at the University of Maryland in Baltimore, while neither prospective nor randomized, has given further insights into the potential of this agent.²⁹ Use of the drug was limited to patients who, after review by a gatekeeper, 1) demonstrated active bleeding, 2) were deemed to have exhausted conventional therapy, and 3) had a reasonable chance of survival. Among the 81 patients who received rVIIa, 61 patients demonstrated sustained improvement in their coagulation status, and 20 patients had persistent coagulopathy and were deemed nonresponders. Among responders, blood product use decreased significantly following the drug, compared with nonresponders. When compared with historical controls matched for severity of injury, use of rFVIIa did not appear to confer any survival advantage, but definitive conclusions must be deferred until a prospective, randomized trial of adequate size can be conducted. Patients receiving rFVIIa for acute hemorrhagic shock (initial dose, 100 mcg/kg) were more likely to require a second dose than patients receiving rFVIIa for other reasons. Of note, patients who did not respond to rFVIIa were significantly more acidotic than responders. This is in keeping with

the in vitro findings of Meng et al,¹⁰ who demonstrated that rFVIIa, like the endogenously generated factor, loses activity in the presence of acidosis. Thus, rFVIIa may not be helpful in stopping bleeding in the trauma patient until acidosis is corrected. Additionally, Dutton et al²⁹ found that responders had higher platelet counts at the time of rFVIIa administration, and they stressed the need for a platelet count $>50,000/\mu\text{L}$ for the activity of rFVIIa to be optimum. None of the 81 patients developed pathologic clots (such as pulmonary embolism, stroke, vascular graft occlusion) within 1 week of their treatment with rFVIIa, and in autopsies performed on 11 of the 46 patients who expired, no evidence of diffuse microvascular thrombosis was noted. However, the safety profile in this patient population will be an important part of future prospective trials.

Trauma and Disseminated Intravascular Coagulation

Disseminated intravascular coagulation is a clinicopathologic state that may arise from a number of clinical conditions; however, sepsis and multiple trauma are the most frequent causes. The underlying pathophysiology of DIC involves widespread systemic activation of coagulation, leading to thrombotic obstruction of small and mid-sized vessels.³⁰ This indiscriminate thrombus formation may compromise the blood supply to various organs, ultimately resulting in multiple organ dysfunction syndrome (MODS). If DIC continues unabated, however, the consumption of clotting factors by formation of fibrin-platelet clots can outstrip liver and marrow synthesis, depleting coagulation factors, protease inhibitors, and platelets, thereby setting the patient at risk for bleeding. Consequently, the patient with DIC may present a picture dominated either by microvascular thrombosis and organ failure or, alternatively, life-threatening bleeding, or both. Disseminated intravascular coagulation tends to be viewed differently by different medical specialists; it is regarded by surgeons as primarily a bleeding disorder, and intensivists are more attuned to microvascular thrombotic complications.

Disseminated intravascular coagulation that stems from sepsis has been thoroughly researched using reproducible animal models. Whether the challenge is *Escherichia coli* (live or killed), or purified lipopolysaccharide (LPS, also known as endotoxin), many of the responses that follow are consistent and dose-dependent. Investigations administering low-dose LPS to human volunteers and higher LPS doses to primates have provided insight into the balance of coagulant and inflammatory mediators that are activated in both compensated and overt DIC.³¹⁻³⁵ Trauma-related DIC, by contrast, is considerably more difficult to encompass within a single animal model; trauma-related DIC has the potential to include tissue injury, variable blood loss, hypotension, acidosis, and secondary challenges such as contamination with fecal matter or thromboplastin-rich brain tissue. Remarkably, despite the differences in their initiation, the pathophysiologic changes of DIC associated with sepsis and trauma are more similar than dissimilar. Indeed, recent studies suggest that many of the same features that represent poor prognostic markers in septic DIC also predict worse outcome in trauma-related DIC.

Four pathophysiologic systems are engaged during DIC, and the magnitude and balance of their responses determines whether the homeostatic challenge is resolved or whether the patient eventually succumbs to complications of this systemic disorder. The following discussion will accordingly use animal models of either LPS-induced or trauma-induced DIC, as well as studies of LPS administration to human volunteers, to develop insights into the interplay between these four systems in the pathophysiology of DIC. The subsequent discussion will focus on investigations of trauma patients for that specific pathophysiology. Readers should bear in mind that,

particularly in trauma cases involving spillage of abdominal contents, the lines between sepsis-induced and trauma-induced DIC may be blurred.

The Cytokine Response. One of the earliest responses in DIC resulting from trauma or LPS is the elaboration of cytokines by stimulated leukocytes and endothelial cells. Cytokines are small proteins that modulate activity in the microenvironment of the releasing cell, and are barely detectable in the normal circulation. However, in response to a major systemic insult, such as trauma or sepsis, their levels can increase significantly and their impact can be manifest body-wide.³⁶ Tumor necrosis factor- α (TNF- α) and interleukin-1 (IL-1), appearing over the first 2 to 3 hours after LPS challenge, appear to be particularly important contributors to many of the findings of DIC.^{33,35,36} Indeed, administration of these recombinant cytokines by themselves elicits many of the characteristics of overt DIC, including its procoagulant effects.^{35,37,38}

The role of individual cytokines in producing organ damage and tissue injury associated with DIC has been assessed using neutralizing antibodies and recombinant receptor antagonists in animal models. Inhibition of TNF- α by anti-TNF antibody was highly protective against lethality when given before an LD100 dose of LPS or live bacteria.³⁹ However, the incomplete response to cytokine antagonists in human DIC trials may result from the inability to intervene at a sufficiently early stage to derive full benefit from these agents.^{40,41} In addition, given that DIC is the final common pathway of activation of multiple systems, effective treatment may entail targeting more than a single entity or system.⁴² Interleukin-6 is another cytokine that appears to play a modulatory, albeit controversial, role in the development of DIC. Unlike TNF- α and IL-1, administration of recombinant IL-6 stimulates only the procoagulant symptoms of DIC,³¹ and in a primate model of DIC, coadministration of anti-IL-6 antibodies attenuated the coagulation activation induced by LPS administration.⁴³ However, IL-6 knock-out mice are not protected from lethal *E.coli* challenge,⁴⁴ suggesting a contributing, but not primary, role for IL-6 in the manifestations of DIC.

In the setting of severe trauma, the cytokine response occurs early and may be an important determinant of which patients go on to develop DIC. Gando et al⁴⁵ measured serial cytokine levels in 58 trauma patients, 22 of whom developed DIC. In blood samples taken within the first 12 hours of arrival to the emergency department, patients with DIC demonstrated significantly higher levels of TNF- α

and IL-1 than did trauma patients who did not develop DIC (Fig. 3). The cause of these cytokine increases is unclear: as a group, DIC patients also exhibited higher injury severity scores than non-DIC patients; however mean arterial blood pressure on arrival to the emergency department did not correlate with cytokine levels, suggesting that hypotension alone was not responsible for their elevation. The DIC patients maintained significantly higher levels of both TNF- α and IL-1 over the 5 days following admission and, as a group, exhibited a greater incidence of acute respiratory distress syndrome, MODS, and death than the non-DIC group.⁴⁵ Whether these persistently elevated cytokines can be attributed to the injury severity, the specific organs involved, the patient's genetic make-up, or some combination of the three is not presently known.

The Coagulation Response. In DIC, coagulation activation is initiated by tissue factor (TF, also known as thromboplastin).⁴⁶ This transmembrane glycoprotein, expressed constitutively on fibroblasts, macrophages, and pericytes in the subendothelium, is not normally in contact with circulating blood elements. Stimulation of monocytes by LPS causes them to express the procoagulant TF on their surface, both from preformed encrypted sites and de novo synthesis.⁴⁶ Indeed, low-dose LPS in healthy subjects causes a 125-fold increase in TF mRNA in blood monocytes.⁴⁷ The same cytokines noted previously, TNF- α , IL-1 β , and IL-6, promote TF expression by LPS-stimulated monocytes.³⁶

Multiple trauma generates extensive and early activation of the TF-initiated coagulation pathway (Fig. 4). Compared with sepsis patients, trauma patients exhibit higher levels of the thrombin-AT complex at the time of admission to the intensive care unit.⁴⁸ Unquestionably, traumatic injuries causing blood exposure to TF-expressing subendothelial cells provide an ample TF supply for localized coagulation.⁴⁶ However, even on the day they present to the emergency department, trauma patients have TF-expressing monocytes in their circulation,⁴⁹ and soluble TF present in their plasma as well.⁵⁰

Endothelial cells (EC) can also be stimulated to synthesize TF, although the role of endothelial cell-derived TF for in vivo procoagulant events has recently been called into question.⁴⁶ Evidence is mounting that TF on monocytes and on monocyte-derived microparticles is an important initiator in the development of DIC.^{51,52} Monocytes and monocyte-derived microparticles are also capable of expressing the negatively charged phospholipids,

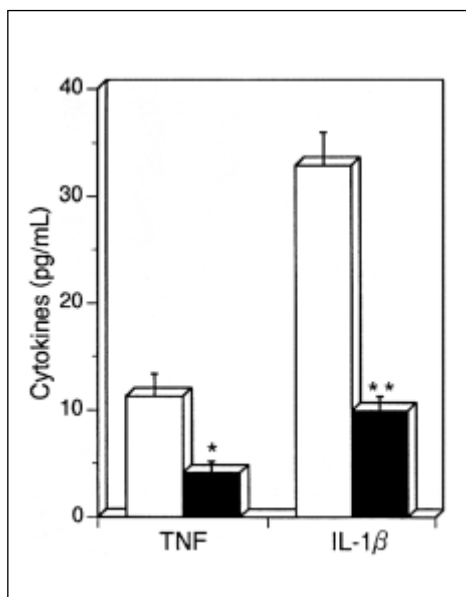


Figure 3. Tumor necrosis factor- α (TNF) and interleukin-1- β (IL-1 β) concentrations in the DIC patient (open bars) and in the non-DIC patients (solid bars). The concentrations of the two cytokines were significantly increased in the DIC patients. * $P = 0.0064$; ** $P = 0.0001$ vs. non-DIC patients. (Reproduced with permission from Gando et al.⁴⁵)

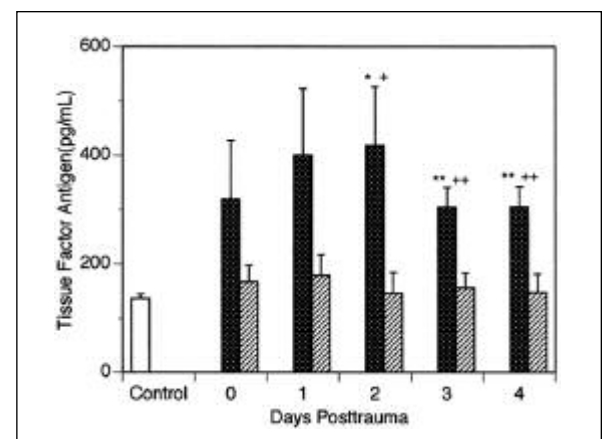


Figure 4. Plasma tissue factor antigen levels after trauma. Patients with DIC (stippled bars, $n = 18$) had increased tissue factor antigen compared with non-DIC patients (hatched bars, $n = 15$) and control subjects (open bar, $n = 10$). Intergroup differences in the time course of tissue factor by two-factor repeated measures analysis was significant ($P = 0.0049$). * $P = 0.05$, ** $P < 0.01$ vs. non-DIC patients; + $P < 0.05$, ++ $P < 0.01$ vs. control subjects. (Reproduced with permission from Gando et al.⁷¹)

essential to activity of the tenase and prothrombinase complexes. Accordingly, the TF-expressing monocyte is capable of coordinating activation of the coagulation cascade on its surface, perhaps facilitated by its ability to bind activated platelets to its surface as well.⁵³ Of potential importance is the fact that the TF-expressing monocyte violates one of the fundamental rules of limited hemostasis, that the procoagulant process should be localized to a specific area of bleeding. The TF-expressing monocyte circulating in the vasculature is not constrained to a site of bleeding and, as such, is not effectively inhibited by endogenous anticoagulants that are largely endothelial cell-associated. Whether or not the TF activity that is expressed by circulating monocytes can complex with (and potentially disseminate) any rFVIIa that is given to control bleeding in the DIC patient is not presently known, but bears investigation.

Thus, virtually on arrival in the emergency department, trauma patients manifest high levels of coagulation activation and the potential for its dissemination by circulating TF-expressing monocytes. Moreover, trauma patients who develop DIC maintain significantly higher plasma TF levels over their first 5 days than trauma patients who do not develop DIC.⁵⁰

The Fibrinolytic System. The fibrinolytic system is activated early in the course of DIC, with D-dimer and other fibrin degradation products increasing coincident with the first clinical manifestations of DIC.⁵⁴ The association between DIC and bleeding is most prominent for clinicians involved in the operative care of DIC patients, and the early appearance of D-dimers in such patients in the past prompted concern for a role of hyperfibrinolysis in DIC. However, it is increasingly clear that true hyperfibrinolysis only rarely complicates DIC; instead, the fibrinolytic response to DIC is actually protective, particularly in preventing the multiorgan failure that often complicates DIC.⁵⁵ When Asakura et al⁵⁶ used tranexamic acid to suppress D-dimer formation in an animal model of LPS-induced DIC, they found it produced a marked exacerbation of DIC.

The administration of LPS to healthy volunteers has given a more accurate picture of the balance between profibrinolytic and antifibrinolytic systems activated during DIC.^{33,35} Challenge with intravenous LPS causes a prompt increase in release of tissue plasminogen activator from stimulated EC (Fig. 5, top). Accelerated by the fibrin generated by concurrent procoagulant processes, plasmin is formed, and then just as rapidly inactivated by the circulating α_2 -antiplasmin that helps keep fibrinolysis in check (Fig. 5, bottom). Plasmin-antiplasmin complexes peak as early as 120 minutes after LPS dosing. This upswing in fibrinolytic activity is transient, however, and is soon further suppressed by an increase in plasminogen activator inhibitor-1 (PAI-1), which peaks 150 minutes after LPS injection (Fig. 5, top). Injection of recombinant TNF- α alone causes a similar peak-and-valley fibrinolytic response, characterized initially by a fourfold increase in tPA levels at 1 hour, followed by an eightfold increase in PAI-1, and subsequent decreasing levels of t-PA.³⁴

This decrement in fibrinolytic activity in the face of ongoing fibrin formation has been termed "fibrinolytic shutdown"; in patients with DIC, high PAI-1 levels are correlated with the severity of multiple organ failure⁵⁷ and with worse outcome.⁵⁸ As described in the next section, one of the benefits associated with administration of the endogenous anticoagulant-activated protein C may be its ability to antagonize PAI-1, thereby opposing the pathologic fibrinolytic shutdown in DIC.

In trauma patients *without* DIC (Fig. 6, left), plasminogen cleavage (line B) and D-dimer formation (line C) increase in a regulated physiologic response to tissue injury.⁵⁹ Just as physiologic is the slightly delayed appearance of PAI-1 (line D), whose increase is associated with a subsequent decline in plasminogen cleavage and formation of D-dimers, with levels normalizing by days 3 to 5. In

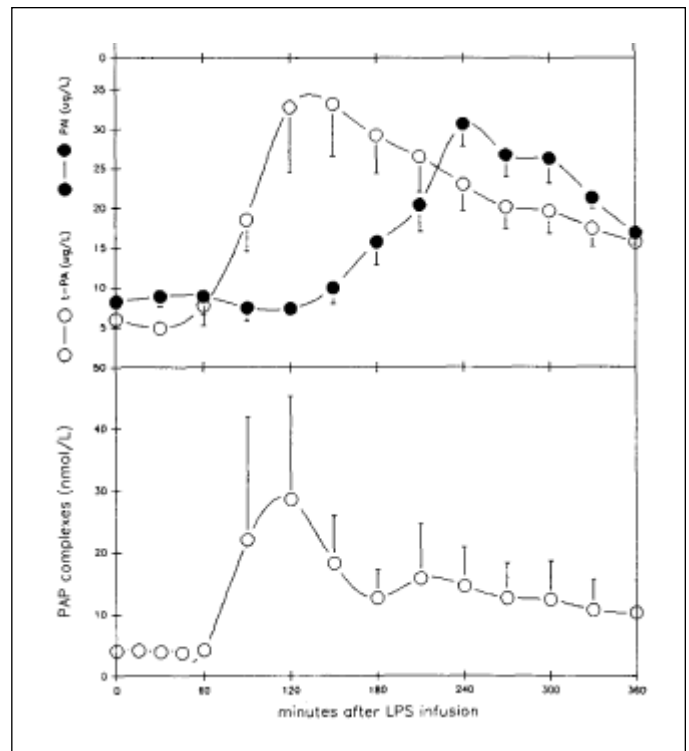


Figure 5. Release of tissue plasminogen activator (top, open circles) and plasminogen activator inhibitor (top, closed circles) and plasmin-antiplasmin complex (bottom, open circles) following LPS administration to human volunteers. Reproduced with permission from van Deventer et al.³⁵

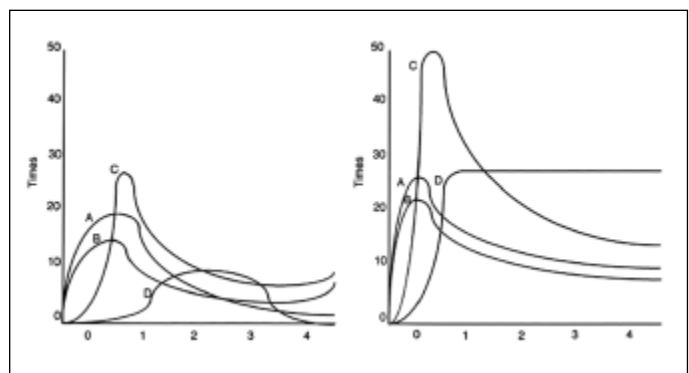


Figure 6. Schematic variation of thrombin activity (Fibrinopeptide A, line A), plasmin activity (Fibrinopeptide B_{β15-42}, line B), fibrin formation (D-dimer, line C), and inhibition of fibrinolysis (PAI-1, line D) after trauma. Patients without DIC (left) and with DIC (right). A vertical axis shows increases from normal values (times). Reproduced with permission from Gando.⁵⁹

contrast, trauma patients *with* DIC (Fig. 6, right) show not only greater activation of coagulation and an exaggerated fibrinolytic response, but also a striking and sustained elevation in PAI-1. Plasminogen cleavage (line B) and D-dimer formation (line C) show the expected decrease in response to PAI-1 elevation (line D), but instead of dropping in parallel to the decline in fibrinolysis, PAI-1 levels remain elevated. Gando et al⁶⁰ demonstrated that high levels of PAI-1 persisted out to 3 to 5 days after trauma and were predictive of the development of acute respiratory distress syndrome, DIC, and death (Fig. 7). Thus, fibrinolytic shutdown after trauma is associated with DIC, MODS, and fatal outcome.

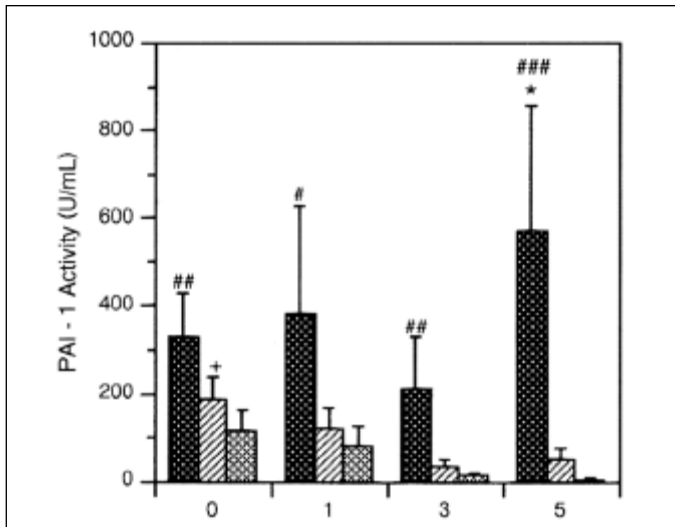


Figure 7. Changes in PAI-1 activity in patients with acute respiratory distress syndrome (dark stippled bars), patients at risk for acute respiratory distress syndrome (hatched bars), and control patients (double-hatched bars) after trauma. # $P < 0.05$, ## $P < 0.01$, ### $P < 0.001$; vs. control patients; * $P < 0.05$ vs. patients at risk; + $P < 0.05$ vs. control patients. Reproduced with permission from Gando et al.⁶⁰

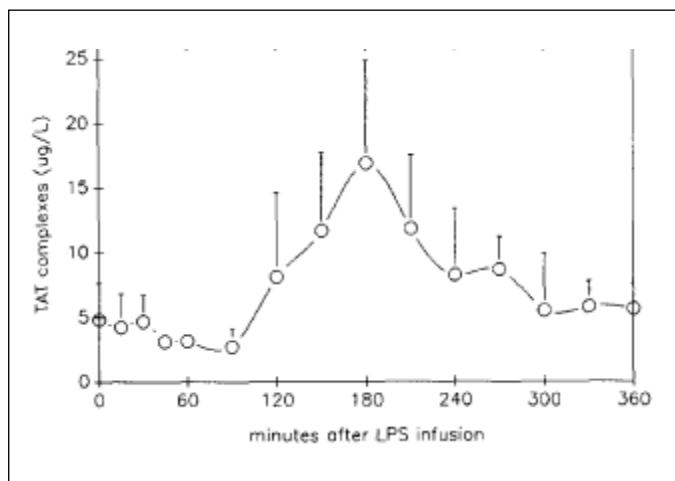


Figure 8. Release of thrombin-antithrombin complex following LPS administration to human volunteers. Reproduced with permission from van Deventer et al.³⁵

The Endogenous Anticoagulant Response. Among endogenous anticoagulants, the first responder to the procoagulant state is the direct thrombin antagonist, antithrombin (AT, also known as antithrombin III). Thrombin-AT complexes are increased as early as 2 hours after LPS injection into healthy human volunteers (Fig. 8).³⁵ Under circumstances of normal hemostasis, AT is present at over twice the concentration ($3.2 \mu\text{mol/L}^{-1}$) of the highest local thrombin concentration reached during clotting ($1.4 \mu\text{mol/L}^{-1}$). Thus, in the absence of the protection conferred by the platelet membrane, any circulating thrombin is inhibited by plasma levels of AT with a half-life < 1 minute. Unfortunately, as DIC develops, AT levels fall, and the ability to block circulating thrombin is diminished. Reduced AT levels have been shown to predict poor outcome in DIC studies.⁶¹ The inability of endogenous AT to keep pace with the rate of thrombin generation during DIC is likely a combination of

consumption (AT binds thrombin with 1:1 stoichiometry, and the complex is cleared, making that AT molecule unavailable for recycling), and reduced liver biosynthesis, which is suppressed by the high circulating cytokine levels.

High levels of thrombin-AT complex form in trauma patients,⁴⁸ along with a consumptive decrease in free AT levels.⁶² The magnitude of the fall in AT levels correlates well with trauma severity.⁶³⁻⁶⁵ Disappointingly, although AT supplementation has shown promise in animal models of DIC,⁶⁶ in vivo AT supplementation of trauma patients does not reduce mortality or length of stay in the intensive care unit.⁶⁵ This lack of success could reflect target dosing; levels of 140% of normal were achieved, but animal studies suggest that $>200\%$ of normal is needed for minimum efficacy.⁶⁶

Another endogenous anticoagulant, tissue factor pathway inhibitor (TFPI), acts early in the coagulation cascade against FXa and the tissue factor-VIIa complex. The TFPI is synthesized in EC, and is constitutively released by EC into the microvasculature.⁶⁷ Under normal conditions, TFPI is largely localized to the endothelial surface by binding to EC-associated glycosaminoglycans, and can be displaced from this site by heparin. The TFPI has direct activity only against FXa, but following exposure to FXa, it acquires activity against the TF-FVIIa complex. Thus, this inhibitor requires some basal coagulation activation to attain full anticoagulant activity, but once activated it is able to inhibit the enzymes that initiate coagulation.⁶⁸ The role of TFPI in preventing development of DIC was demonstrated in a baboon model of sepsis, where recombinant TFPI abrogated the mortality of a lethal dose of *E. coli*.⁶⁹

The importance of TFPI in antagonizing trauma-induced DIC was suggested by an animal model of procoagulant DIC; TFPI depletion sensitized rabbits to DIC development after TF injection.⁷⁰ In actual trauma patients, however, Gando et al⁷¹ demonstrated that, although patients who developed DIC had significantly higher TF levels than non-DIC patients, the levels of TFPI did not increase in proportion either to the TF levels or to severity of DIC. Whether this ceiling on TFPI represents a true peak in the levels attainable in vivo, or whether DIC-associated mediators suppress maximal TFPI biosynthesis, is not presently known. Clinical trials testing the efficacy of recombinant TFPI supplementation in DIC are presently being conducted.

Activated protein C (APC) is an endogenous protein whose combined anticoagulant, anti-inflammatory, and profibrinolytic properties make it an important regulator in the defense against DIC.⁷² As with TFPI, the protein C system becomes activated only after coagulation is under way. Formed thrombin binds to thrombomodulin, a proteoglycan associated with endothelial cell surfaces. Once bound, thrombin loses its ability to activate platelets and, instead, activates protein C. Unactivated protein C is tethered to the EC surface by endothelial cell protein C receptor (EPCR), which posits it for activation by the adjacent thrombomodulin-bound thrombin.⁷³ The APC checks down the procoagulant process by inactivating factors VIIIa and Va, critical components of the tenase and prothrombinase complexes, respectively, in a reaction that is also enhanced by EPCR and protein S. In addition, APC complexes with PAI-1, and thereby can block the fibrinolytic shutdown previously described. Along with these anticoagulant and profibrinolytic activities, APC has anti-inflammatory properties as well.⁷² Recombinant APC given to LPS-challenged rats resulted in reduced TNF- α production, and protein C-deficient mice (heterozygous) exhibited higher levels of proinflammatory cytokines on systemic endotoxemia.

DIC affects the APC system in multiple ways. In baboons given *E. coli*, soluble thrombomodulin (STM) levels rose progressively, indicating ongoing endothelial cell injury.³² Coincident with this rise

in sTM, peaking between 6 and 12 hours, was a dramatic decline in levels of the APC-protein C inhibitor complex, suggesting a decrease in APC generation. In an analogous fashion in humans, patients with severe meningococcal sepsis demonstrated high plasma levels of sTM, coincident with low EC-associated levels of both TM and EPCR in skin biopsies. It is noteworthy that recombinant APC is the first hemostatic agent to demonstrate any survival benefit in humans with severe sepsis.⁷⁴ The combination of anticoagulant, anti-inflammatory, and profibrinolytic activity of this agent is a likely contributor to its success.

The physiology of APC in trauma-related DIC has not yet received the degree of attention it has achieved in septic DIC. Trauma patients demonstrate high baseline levels of soluble thrombomodulin⁴⁸ and low levels of protein C, the latter in inverse proportion to injury severity,⁶² suggesting that this endogenous anticoagulant pathway is engaged and consumed early in the posttrauma period. Both protein C activity and antigen levels have been found to be significantly lower in trauma patients with DIC than in trauma patients who did not develop DIC, and low levels were predictive of fatal outcome.⁷⁵ Soluble thrombomodulin levels are also increased in trauma patients who develop DIC and/or MODS, and these levels also predict fatality.⁷⁶ These findings suggest that, as with sepsis-induced DIC, protein C is activated early after trauma, and may be important in determining which patients ultimately develop DIC.

Whether recombinant APC (rAPC) might confer some of the same benefits in posttrauma DIC as it does in sepsis-associated DIC is not yet known. Bleeding is the major safety concern associated with use of this agent in all patients. However, a post hoc review of the subset of postsurgical patients in the multicenter trial of rAPC (PROWESS trial) by a team of surgeons showed a surprisingly positive risk-benefit ratio.⁷⁷ Of the 1,690 patients enrolled in the PROWESS trial, 28% were surgical patients who underwent an operative procedure within 30 days, some as early as within 12 hours, of study entry. For the surgical cohort as a whole, treatment with rAPC was associated with a 10% relative risk reduction for 28-day mortality, and a 21% reduction in high-risk patients as defined by APACHE II scores of 25 or greater. Moreover, although rAPC administration was associated with an increased overall risk of serious bleeding *during the infusion process*, surgical patients were not at higher risk than nonsurgical patients for this complication. Additionally, 90% of the drug is eliminated within 2 hours after discontinuation of the infusion, presumably making anticoagulant effects spontaneously reversible in short order.

In summary, DIC develops when toxic levels of cytokines such as TNF- α , IL-1 β , and IL-6 and systemic activation of procoagulant pathways culminate in widespread fibrin deposition in the microvasculature. The combined proinflammatory and procoagulant activity is on so massive a scale that endogenous anticoagulants such as AT, TFPI, and APC are overwhelmed, and efforts to keep the fibrin-occluded microvasculature patent by fibrinolytic activity are frustrated by elevated and sustained production of the endogenous antagonist, PAI-1. The imbalance in these processes that are normally so carefully orchestrated may culminate in vasculopathy, leading to multiorgan failure and bleeding as the result of consumptive depletion of coagulation factors.

Conclusions

Trauma patients present a significant hemostatic challenge distinct from their injuries. Their clinical picture, especially early on, is often dominated by a bleeding coagulopathy that appears refractory to transfusion therapy. The importance of hypothermia and acidosis, in

particular, to the development of this direct coagulopathy is increasingly appreciated, as is the inability of transfused blood components to achieve hemostasis in cold, acidotic tissues. By contrast, the development of DIC in the trauma patient is a consequence of imbalance in the activation of coagulant, inflammatory, anticoagulant, and fibrinolytic systems. It is not yet known whether the patient with early coagulopathy is more or less likely to eventually develop DIC. Certainly, greater severity of injury predisposes to both of these complications. The potential for overlap to occur between trauma-associated coagulopathy and DIC may be critical to the safe use of drugs such as rFVIIa, where injudicious administration or dosing may have the potential to tip a patient with modest coagulopathy into a DIC-like consumptive coagulopathy. Well-controlled, large clinical trials are needed to assess hemostatic therapy in trauma coagulopathy and DIC. Based on the pathophysiology noted here, it is also likely that multimodality therapies may be needed to achieve efficacy in such trials. Until then, clinicians are limited to supportive therapy with appropriate resuscitation fluids, blood products, and close monitoring of the available parameters of platelets, fibrinogen, and plasma coagulation factors.

References

- Counts RB, Haisch C, Simon TL, et al. Hemostasis in massively transfused trauma patients. *Ann Surg* 1979;190:91-9.
- Ciavarella D, Reed RL, Counts RB, et al. Clotting factor levels and the risk of diffuse microvascular bleeding in the massively transfused patient. *Br J Haematol* 1987;67:365-8.
- Cosgriff N, Moore EE, Sauaia A, et al. Predicting life-threatening coagulopathy in the massively transfused trauma patient: Hypothermia and acidosis revisited. *J Trauma* 1997;42:857-62.
- Lynn M, Jeroukhimov I, Klein Y, Martinowitz U. Updates in the management of severe coagulopathy in trauma patients. *Intensive Care Med* 2002;28(suppl 2):S241-7.
- Parr MJA, Alabdi T. Damage control surgery and intensive care. *Injury* 2004;35:713-22.
- Peng RY, Bongard FS. Hypothermia in trauma patients. *J Am Coll Surg* 1999;188:685-96.
- Jurkovich GJ, Greiser WB, Luterman A, et al. Hypothermia in trauma victims: an ominous predictor of survival. *J Trauma* 1987;27:1019-24.
- Wolberg AS, Meng ZH, Monroe DM 3rd, et al. A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. *J Trauma* 2004;56:1221-8.
- Watts DD, Trask A, Soeken K, et al. Hypothermic coagulopathy in trauma: effect of varying levels of hypothermia on enzyme speed, platelet function, and fibrinolytic activity. *J Trauma* 1998;44:846-54.
- Meng ZH, Wolberg AS, Monroe DM, et al. The effect of temperature and pH on the activity of factor VIIa: implications for the efficacy of high-dose factor VIIa in hypothermic and acidotic patients. *J Trauma* 2003;55:886-91.
- Kaplan LJ, Kellum JA. Initial pH, base deficit, lactate, anion gap, strong ion difference, and strong ion gap predict outcome from major vascular injury. *Crit Care Med* 2004;32:1120-4.
- Siffert W. Regulation of platelet function by sodium-hydrogen exchange. *Cardiovasc Res* 1995;29:160-6.
- Gende OS. Capacitative calcium influx and intracellular pH cross-talk in human platelets. *Platelets* 2003;14:9-14.
- Luzzatto G, Kroll MH, Zavoico GB, et al. Regulation of the phosphoinositide cycle by Na⁺/H⁺ exchange and intracellular pH in human platelets. *Biochim Biophys Acta* 1991;1084:78-86.
- De Cristofaro R, Landofì R, Di Cera E, et al. Inhibition of fibrinogen binding to human platelets by blockade of Na⁺/H⁺ exchange. *Biochem Biophys Res Comm* 1989;161:1228-32.
- Sweatt JD, Blair IA, Cragoe EJ, et al. Inhibitors of Na⁺/H⁺ exchange block epinephrine- and ADP-induced stimulation of human platelet phospholipase C by blockade of arachidonic acid release at a prior step. *J Biol Chem* 1986;261:8660-6.
- Rinder CS, Student LA, Bonan JL, et al. Aspirin does not inhibit adenosine diphosphate-induced platelet alpha-granule release. *Blood* 1993;82:505-12.
- Rinder HM, Snyder EL, Tracey JB, et al. Reversibility of severe metabolic stress in stored platelets after in vitro rescue or in vivo transfusion: restoration of secretory function and maintenance of platelet survival. *Transfusion* 2003;43:1230-7.

19. Sims C, Seigne P, Menconi M, et al. Skeletal muscle acidosis correlates with the severity of blood volume loss during shock and resuscitation. *J Trauma* 2001;51:1137-46.
20. Dieterich HJ. Recent developments in European colloid solutions. *J Trauma* 2003;54(5 suppl):S26-30.
21. Treib J, Haass A, Pindur G. Coagulation disorders caused by hydroxyethyl starch. *Thromb Haemost* 1997;78:974-83.
22. Wilder DM, Reid TJ, Bakaltcheva IB. Hypertonic resuscitation and blood coagulation: in vitro comparison of several hypertonic solutions for their action on platelets and plasma coagulation. *Thromb Res* 2002;107:255-61.
23. Wong DW, Mishkin FS, Tanaka TT. The effects of bicarbonate on blood coagulation. *JAMA* 1980;244:61-2.
24. DeLoughery TG. Coagulation defects in trauma patients: etiology, recognition, and therapy. *Crit Care Clin* 2004;20:13-24.
25. Whitten CW, Greilich PE. Thromboelastography: past, present, and future [comment]. *Anesthesiology* 2000;92:1223-5.
26. Kaufmann CR, Dwyer KM, Crews JD, et al. Usefulness of thromboelastography in assessment of trauma patient coagulation. *J Trauma* 1997;42:716-22.
27. DeJgaard A. Update on Novo Nordisk's clinical trial programme on NovoSeven®. *Blood Coagul Fibrinolysis* 2003;14(suppl 1):S39-41.
28. Barletta JF, Ahrens CL, Tyburski JG, Wilson RF. A review of recombinant Factor VII for refractory bleeding in nonhemophilic trauma patients. *J Trauma* 2005;58:646-51.
29. Dutton RP, McCunn M, Hyder M, et al. Factor VIIa for correction of traumatic coagulopathy. *J Trauma* 2005;57:709-19.
30. Levi M, de Jonge E, van der Poll T, et al. Advances in the understanding of the pathogenetic pathways of disseminated intravascular coagulation result in more insight in the clinical picture and better management strategies. *Semin Thromb Hemost* 2001;27:569-75.
31. Stouthard JM, Levi M, Hack CE, et al. Interleukin-6 stimulates coagulation, not fibrinolysis, in humans. *Thromb Haemost* 1996;76:738-42.
32. Taylor FB, Wada H, Kinasewitz G. Description of compensated and uncompensated disseminated intravascular coagulation (DIC) responses (non-overt and overt DIC) in baboon models of intravenous and intraperitoneal *Escherichia coli* sepsis and in the human model of endotoxemia: toward a better definition of DIC. *Crit Care Med* 2000;28(suppl):S12-9.
33. Taylor FB, Haddad PA, Hack E, et al. Two-stage response to endotoxin infusion into normal human subjects: correlation of blood phagocyte luminescence with clinical and laboratory markers of the inflammatory, hemostatic response. *Crit Care Med* 2001;29:326-34.
34. van der Poll T, Levi M, Buller HR, et al. Fibrinolytic response to tumor necrosis factor in healthy subjects. *J Exp Med* 1991;174:729-32.
35. van Deventer S, Buller HR, ten Cate JW, et al. Experimental endotoxemia in humans: analysis of cytokine release and coagulation, fibrinolytic, and complement pathways. *Blood* 1990;76:2520-6.
36. van der Poll T, de Jonge E, Levi M. Regulatory role of cytokines in disseminated intravascular coagulation. *Semin Thromb Hemost* 2001;27:639-51.
37. Okusawa S, Gelfland JA, Ikejima T, et al. Interleukin 1 induces a shock-like state in rabbits. Synergism with tumor necrosis factor and the effect of cyclooxygenase inhibition. *J Clin Invest* 1988;81:1162-72.
38. Tracey KJ, Beutler B, Lowry SF, et al. Shock and tissue injury induced by recombinant human cachectin. *Science* 1986;234:470-4.
39. van der Poll T, Jansen PM, Van Zee KJ, et al. Pretreatment with a 55-kDa tumor necrosis factor receptor-immunoglobulin fusion protein attenuates activation of coagulation, but not of fibrinolysis, during lethal bacteremia in baboons. *J Infect Dis* 1997;176:296-9.
40. Fisher CJ Jr, Dhainaut JF, Opal SM, et al. Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. Results from a randomized, double-blind, placebo-controlled trial. Phase III rIL-1ra Sepsis Syndrome Study Group. *JAMA* 1994;271:1836-43.
41. Abraham E, Wunderink R, Silverman H, et al. Efficacy and safety of monoclonal antibody to human tumor necrosis factor- α in patients with sepsis syndrome. A randomized, controlled, double-blind, multicenter clinical trial. TNF- α MAb Sepsis Study Group. *JAMA* 1995;273:934-41.
42. Reinhart K, Karzai W. Anti-tumor necrosis therapy in sepsis: update on clinical trials and lessons learned. *Crit Care Med* 2001;29(suppl):S121-5.
43. van der Poll T, Levi M, Hack CE, et al. Elimination of interleukin 6 attenuates coagulation activation in experimental endotoxemia in chimpanzees. *J Exp Med* 1994;179:1253-9.
44. Fattori E, Cappelletti M, Costa P, et al. Defective inflammatory response in interleukin-6-deficient mice. *J Exp Med* 1994;180:1243-50.
45. Gando S, Nakanishi Y, Tede I. Cytokines and plasminogen activator inhibitor-1 in posttrauma disseminated intravascular coagulation: relationship to multiple organ dysfunction syndrome. *Crit Care Med* 1995;23:1835-42.
46. Osterud B, Bjorklid E. The tissue factor pathway in disseminated intravascular coagulation. *Semin Thromb Hemost* 2001;27:605-17.
47. Franco RF, de Jonge E, Dekkers PE, et al. The in vivo kinetics of tissue factor messenger RNA expression during human endotoxemia: relationship with activation of coagulation. *Blood* 2000;96:554-9.
48. Boldt J, Papsdorf M, Rothe A, et al. Changes of the hemostatic network in critically ill patients: is there a difference between sepsis, trauma, and neurosurgery patients? *Crit Care Med* 2000;28:445-50.
49. Utter GH, Owings JT, Jacoby RC, et al. Injury induces increased monocyte expression of tissue factor: factors associated with head injury attenuate the injury-related monocyte expression of tissue factor. *J Trauma* 2002;52:1071-7.
50. Gando S, Nanzaki S, Morimoto Y, et al. Systemic activation of tissue-factor dependent coagulation pathway in evolving respiratory distress syndrome in patients with trauma and sepsis. *J Trauma* 1999;47:719-23.
51. Nieuwland R, Berckmans RJ, McGregor S, et al. Cellular origin and procoagulant properties of microparticles in meningococcal sepsis. *Blood* 2000;95:930-5.
52. Osterud TB. Increased tissue thromboplastin activity in monocytes of patients with meningococcal infection: related to an unfavorable prognosis. *Thromb Haemost* 1983;59:5-7.
53. Monroe DM, Hoffman M, Roberts HR. Transmission of a procoagulant signal from tissue factor-bearing cell to platelets. *Blood Coagul Fibrinolysis* 1996;7:459-64.
54. Kario K, Matsuo T, Kodama K, et al. Imbalance between thrombin and plasmin activity in disseminated intravascular coagulation. Assessment by the thrombin-antithrombin III complex/plasmin- α -2-antiplasmin complex ratio. *Haemostasis* 1992;22:179-86.
55. Hack CE. Fibrinolysis in disseminated intravascular coagulation. *Semin Thromb Hemost* 2001;27:633-8.
56. Asakura H, Sano Y, Omote M, et al. Significance of decreased plasma D-dimer levels following lipopolysaccharide-induced disseminated intravascular coagulation in rats. *Int J Hematol* 2004;79:394-9.
57. Asakura H, Jokaji H, Saito M, et al. Study of the balance between coagulation and fibrinolysis in disseminated intravascular coagulation using molecular markers. *Blood Coagul Fibrinolysis* 1994;5:829-32.
58. Mesters RM, Florke N, Ostermann H, et al. Increase of plasminogen activator inhibitor levels predicts outcome of leukopenic patients with sepsis. *Thromb Haemost* 1996;75:902-7.
59. Gando S. Disseminated intravascular coagulation in trauma patients. *Semin Thromb Hemost* 2001;27:585-95.
60. Gando S, Kameue T, Nanzaki S, et al. Increased neutrophil elastase, persistent intravascular coagulation, and decreased fibrinolytic activity in patients with posttraumatic acute respiratory distress syndrome. *J Trauma* 1997;42:1068-72.
61. Mammen EF. Antithrombin: its physiological importance and role in DIC. *Semin Thromb Hemost* 1998;24:19-25.
62. Engelman DT, Gabram S, Allen L, et al. Hypercoagulability following multiple trauma. *World J Surg* 1996;20:5-10.
63. Miller RS, Weatherford DA, Stein D, et al. Antithrombin III and trauma patients: factors that determine low levels. *J Trauma* 1994;37:442-5.
64. Liener UC, Bruckner UB, Strecker W, et al. Trauma severity-dependent changes in AT III activity. *Shock* 2001;15:344-7.
65. Waydhas C, Nast-Kolb D, Gippner-Steppert C, et al. High-dose antithrombin III treatment of severely injured patients: results of a prospective study. *J Trauma* 1998;45:931-40.
66. Taylor FB, Emerson TE, Jordan R, et al. Antithrombin III prevents the lethal effects of *Escherichia coli* infusion in baboons. *Circ Shock* 1998;26:227-35.
67. Osterud B, Bajaj MS, Bajaj SP. Sites of tissue factor pathway inhibitor (TFPI) and tissue factor expression under physiologic and pathologic conditions. On behalf of the Subcommittee on Tissue Factor Pathway Inhibitor (TFPI) of the Scientific and Standardization Committee of the ISTH. *Thromb Haemost* 1995;73:873-5.
68. Doshi SN, Marmur JD. Evolving role of tissue factor and its pathway inhibitor. *Crit Care Med* 2002;30(suppl):S241-50.
69. Creasey AA, Chang AC, Feigen L, et al. Tissue factor pathway inhibitor reduces mortality from *Escherichia coli* septic shock. *J Clin Invest* 1993;91:2850-60.
70. Sandset PM, Warn-Cramer CB, Rao LV, et al. Depletion of extrinsic pathway inhibitor (EPI) sensitizes rabbits to disseminated intravascular coagulation induced with tissue factor: evidence supporting a physiologic role for EPI as a natural anticoagulant. *Proc Natl Acad Sci U S A* 1991;88:708-12.
71. Gando S, Nanzaki S, Morimoto Y, et al. Tissue factor pathway inhibitor response does not correlate with tissue factor-induced disseminated intravascular coagulation and multiple organ dysfunction syndrome in trauma patients. *Crit Care Med* 2001;29:262-6.

72. Faust SN, Heyderman RS, Levin M. Coagulation in severe sepsis: a central role for thrombomodulin and activated protein C. *Crit Care Med* 2001;29 (7 suppl):S62-8.
73. Esmon CT. Protein C anticoagulant pathway and its role in controlling microvascular thrombosis and inflammation. *Crit Care Med* 2001;29 (7 suppl):S48-52.
74. Dhainaut JF, Laterre PF, LaRosa SP, et al. The clinical evaluation committee in a large multicenter phase 3 trial of drotrecogin alfa (activated) in patients with severe sepsis (PROWESS): role, methodology, and results. *Crit Care Med* 2003;31:2291-301.
75. Gando S. Serial studies of protein C in trauma patients [in Japanese]. *Jpn J Thromb Hemost* 1996;7:312-8.
76. Gando S, Nakanishi Y, Kameue T, et al. Soluble thrombomodulin increases in patients with disseminated intravascular coagulation and in those with multiple organ dysfunction syndrome after trauma: role of neutrophil elastase. *J Trauma* 1995;39:660-4.
77. Barie PS, Williams MD, McCollam JS, et al. Benefit/risk profile of drotrecogin alpha (activated) in surgical patients with severe sepsis. *Am J Surg* 2004;188:212-20.

Intraoperative Blood Conservation—Every Cell is Sacred

Jonathan H. Waters, MD

Department of Anesthesiology
Magee Womens Hospital of
University of Pittsburgh Medical Center
Suite 3510
300 Halket Street
Pittsburgh, PA 15213 USA
watejh@upmc.edu

Learning Objectives: To give the reader an understanding of 1) cell salvage efficiency and how it might be optimized, 2) the use of cell salvage in trauma surgery, and 3) the complications associated with cell salvage and how they might be avoided.

Abstract

Awareness of the negative impact of allogeneic blood transfusion on patient outcome is increasing. Many strategies can be used to minimize or eliminate allogeneic transfusion. These strategies include preoperative anemia optimization, intraoperative hemodilution, point of care laboratory testing, and cell salvage. The technique that offers the greatest blood avoidance ability is cell salvage. This article discusses how cell salvage can be maximized, the safety of this technique in trauma surgery, and the complications associated with its application.

In recent years, an evolving understanding of the consequences of allogeneic blood transfusion has resulted in an interest in blood conservation. This understanding includes a recognition of the immunosuppressive effects of allogeneic transfusion,¹ recognition of the constantly changing risks of transmission of bacterial and viral disease,² and a growing awareness of transfusion-related acute lung injury.³ More recently, interest has focused on the effect of stored blood on the microcirculation. It appears from animal models that

our goal of enhancing oxygen delivery through transfusion may not actually be improving tissue oxygen levels. In these models, functional capillary density and tissue oxygenation actually fall following the transfusion of stored blood.^{4,5} In addition, an allogeneic blood shortage⁶ and rising costs of blood products have made many hospital administrators take note of the impact that allogeneic blood has on their balance sheet.

Multiple strategies can be applied to avoid allogeneic transfusion. The primary strategies involve preoperative erythropoietin and iron supplementation, preoperative autologous donation, acute normovolemic hemodilution, and the application of cell salvage systems. These strategies are outlined in Table 1. From mathematical modeling, it would appear that cell salvage offers the greatest ability to help toward avoiding allogeneic blood transfusion.⁷ In addition, cell salvage requires no preoperative preparation to effectively implement, making it ideal for a trauma or obstetrical hemorrhage.

Mathematical modeling of cell salvage has revealed that small changes in red cell processing efficiency can make large differences in the blood loss that a patient can sustain prior to needing allogeneic transfusion therapy.⁸ These models suggest that a 70-kg patient with a starting hematocrit of 45% and a blood volume of 4,900 mL can sustain a blood loss of 9,600 mL if a transfusion trigger of 21% is used and cell salvage captures 60% of lost red blood cells (Fig. 1). The sustainable blood loss rises to 13,750 mL if 70% red cell recovery is achieved. This implies that a 10% increase in effectively collecting, washing, and returning lost cells results in the ability for a patient to sustain 4,150 mL of greater blood loss without needing allogeneic red cell products. This highlights the importance of optimizing the cell salvage system.

Optimizing Red Cell Return

Optimizing the cell salvage process can occur at multiple points in the processing. The following discussion will elucidate some of the areas where optimization can occur.

Suction. Shear force applied to red cells during suctioning can lead to hemolysis. Shear force is created by turbulence. In general, turbulence destroys red cells. High turbulence results from high suction pressure. So the lowest suction pressure that is tolerable to the surgeon should be applied. The vacuum pressure should be regulated to 80 to 120 torr, which is adequate for most surgical procedures.^{9,10} Vacuum level can be temporarily raised to clear the field in the event of massive blood loss, and then reduced to a lower level for lower flows. It is important to remember that if multiple suction lines are attached to a collection reservoir, all of the lines need to be used simultaneously; otherwise, when one suction line is placed in blood and the others are not, then suction pressure will be reduced. Alternatively, a vigilant cell salvage technician can place clamps on