Inflammatory response to trauma: Implications for coagulation and resuscitation

Albert Pierce and Jean-François Pittet
Department of Anesthesiology, University of Alabama at Birmingham, Birmingham AL

Abstract

Purpose of this review—Recent studies have changed our understanding of the timing and interactions of the inflammatory processes and coagulation cascade following severe trauma. This review highlights this information and correlates its impact on the current clinical approach for fluid resuscitation and treatment of coagulopathy for trauma patients.

Recent findings—Severe trauma is associated with a failure of multiple biologic emergency response systems that includes imbalanced inflammatory response, acute coagulopathy of trauma (ACOT), and endovascular glycocalyx degradation with microcirculatory compromise. These abnormalities are all inter-linked and related. Recent observations show that after severe trauma: 1) pro-inflammatory and anti-inflammatory responses are concomitant, not sequential and 2) resolution of the inflammatory response is an active process, not a passive one. Understanding these interrelated processes is considered extremely important for the development of future therapies for severe trauma in humans.

Summary—Traumatic injuries continue to be a significant cause of mortality worldwide. Recent advances in understanding the mechanisms of end-organ failure, and modulation of the inflammatory response has important clinical implications regarding fluid resuscitation and treatment of coagulopathy.

Keywords
Inflammatory response; immunosuppression; acute traumatic coagulopathy; fluid resuscitation; resolution of inflammation

Introduction

Trauma is the leading cause of death in the United States within the age range of one to forty five years, causing nearly six million deaths per year worldwide (1, 2). This tragic loss of young lives results in a tremendous loss of potential and productivity to society and incalculable loss to family and friends.

Trauma associated tissue injury initiates an inflammatory response and activates the coagulation cascade. Activation of the immune system and the subsequent inflammatory
response is absolutely necessary for healing and defense against pathogens; however, greater magnitude and longer duration as seen with the systemic inflammatory response syndrome (SIRS) is associated with worse outcomes (3, 4). Imbalanced systemic inflammation is the cause of inflammatory complications (5, 6). Regulation of pro-inflammatory and anti-inflammatory processes is therefore especially important and has significant implications regarding coagulation and resuscitation and potential future therapies (7-9).

Trauma patients frequently suffer from blood loss requiring fluid resuscitation to provide essential tissue perfusion. While under-resuscitation leads to tissue hypo-perfusion and prolonged inflammatory response, we also must recognize that fluid resuscitation creates inflammatory consequences of its own (10). This resuscitation must be prompt yet judicious in order to improve the likelihood of a favorable outcome (11-13).

In the present article, we will highlight timing and interactions of the inflammatory processes and coagulation cascade following severe trauma and correlate its impact on the current clinical approach for fluid resuscitation and treatment of coagulopathy for trauma patients.

**Post-traumatic inflammatory response**

The activation of the immune system following trauma is important for protection and healing of damaged tissues. Following severe trauma, the human body responds primarily via activation of the innate immune system in a way that is incredibly similar to other causes of the Systemic Inflammatory Response Syndrome (SIRS) and sepsis (14-17). In fact, bacterial pathogens, burns and direct injury all cause very similar immunologic responses at genomic and transcriptomic levels (14). This contradicts the long held assumption that the post-traumatic SIRS response was bacterial in origin. It is now considered mostly a sterile process (18-21). Recently, it has been shown that the inflammatory response is a synchronous combination of pro-inflammatory and anti-inflammatory processes evident soon after trauma has occurred (14, 16). This changed our thoughts that an initial pro-inflammatory period was followed and tempered by anti-inflammatory processes. Severe injuries are associated with a proportional increase in Interleukin-6 (IL-6) and subsequent responses from the adaptive and innate immune systems (22, 23). Although the greater responsibility for tissue defense and repair falls to the innate immune system, some interesting changes occur in the adaptive immune system including decreased T1:T2 ratios. This diminished adaptive immunity and relative immunosuppression may lead to secondary infections (24-31).

As previously reported for pathogen associated molecular patterns (PAMPs), such as bacterial lipopolysaccharide (LPS), traumatic tissue damage causes intracellular mediators to be released into the extracellular space and circulation at much higher concentrations than typically occurs with programmed cell death (21, 32-34). Some of these mediators act as “alarmins” or damage associated molecular patterns (DAMPs) (32, 34). Mitochondrial DNA (mtDNA), with significant bacterial similarity, is one such DAMP (33, 35). Others include histones, HMGB1, and the heat shock proteins (32, 36).
Pattern recognition receptors (PRRs), such as the Toll-like receptors (TLRs) or RAGE, recognize these PAMPs and DAMPs and subsequently initiate the inflammatory process (32, 36, 37). If this process remains localized to the primary site of infection, normal healing occurs. Damage response systems must remain properly balanced and appropriately timed in order to proceed to the ultimate goal of healing. If this immune response becomes imbalanced and widely systemic with pronounced cytokine amplification, many proceed to the systemic inflammatory response (SIRS), multi-organ failure (MOF) and death (8, 38, 39). Recent data indicate that the resolution of an acute inflammatory response is an active process. It is promoted by anti-inflammatory and pro-resolution mediators such as lipoxins, resolvins, and protectins (40, 41). These recently described mediators may provide new possibilities for control of inappropriately prolonged inflammatory conditions including severe trauma or sepsis (41).

**Relationship between the inflammatory response and coagulation cascade**

Major hemorrhage and its resulting coagulation abnormalities are major concerns to all who care for the severely traumatized patient since severe hemorrhage is considered the largest single cause of death within this patient population during the first 24-48 hours after trauma (42, 43). Post-traumatic inflammation and coagulation cascade are inter-related and interactive; there are multiple examples of this (Figure 1 (44)). Alarmins have been shown to have direct pro-coagulant activity. Examples include histone-induced platelet activation, upregulation of plasminogen activator inhibitor (PAI), and down regulation of thrombomodulin, and histone-DNA complex triggering TLR-2, 4 and 9 activation with the end-result of increased inflammatory cytokine production (36, 45-47). Inflammatory cytokines may also activate platelets and increase their expression of pro-coagulants (48, 49).

Coagulation factors activate the immune system as well. Formation of fibrin can trap bacteria and is associated with decreased bacterial dissemination (50). Also, activated platelets bind neutrophils, inducing formation of antimicrobial neutrophil DNA extracellular traps (NETs) (51). Tissue factor-factor VIIa complex, thrombin, and factor Xa enhance the inflammatory response, while the naturally occurring anti-coagulants, such as activated protein C (aPC), help to limit this increased inflammation (52, 53).

Protein C has been shown to have anticoagulant and anti-inflammatory properties in response to trauma (54). One fourth of severely injured patients exhibit ACOT upon arrival to the hospital (4). This newly described posttraumatic coagulopathy is associated with elevated plasma levels of activated protein C (aPC) and decreased protein C zymogen and is not due to dilution of coagulation factors caused by large fluid resuscitation (4, 53). Furthermore, it is associated with worse outcomes including longer hospital stays and significantly higher mortality (4). Studies with a murine model of trauma-hemorrhage have shown that the early posttraumatic coagulopathy can be corrected by blockade of the anticoagulant domain of aPC (55). However, a complete blockade of the dual anticoagulant and anti-inflammatory properties of aPC led to much higher mortality rate, suggesting an important role for protein C in modulating inflammatory response and coagulation activation after severe trauma (55). For example, within the first six hours after trauma, increased
plasma levels of circulating histones have been shown to be a predictor of mortality in trauma patients (56, 57). Recent research in primates demonstrates that aPC may protect against excessive microvascular thrombosis by cleaving the pro-coagulant extracellular histones associated with endothelial dysfunction, organ failure, and death (47, 56-58). After severe trauma, it is not uncommon to see a hypo- followed by a hypercoagulable state (54). This correlates with initial high levels of aPC with subsequent depletion of its zymogen, and eventually aPC as well (54). We may speculate that future treatments might include the administration of a modified protein C with decreased or absent anticoagulant properties that yet retains endothelial cytoprotective effect (53). Thus, the massive activation of the protein C pathway after severe trauma appears to represent a maladaptive response of an important protective mechanism that prevents microvascular thrombosis and endothelial cell damage. Protection of the endothelium is indeed important because endothelial integrity and homeostasis are critical for tissue perfusion, oxygenation and immune function (59). For example, the endothelial glycocalyx is now seen as an essential component of the vascular barrier (59). Endothelial glycocalyx shedding and endothelial gap junction failure are associated with significant capillary leakage that has a direct impact upon resuscitation and vice-versa (57, 60-62). In an attempt to break this vicious cycle, it is critical to provide adequate fluid resuscitation for perfusion of the microcirculation without increasing blood loss.

**Relationship between inflammatory response and fluid resuscitation**

Resuscitation of the severely traumatized patient has recently received a considerable amount of attention. A large volume crystalloid resuscitation, followed by several units of packed red blood cells then a modest amount of fresh frozen plasma and platelets was accepted as the standard for decades (63). This is no longer considered appropriate. Tissue damage from hypoperfusion is worsened by edema and linked to a systemic inflammatory response in a circular pattern (Figure 2).

A patient with significant tissue injury and concomitant hypovolemic shock exhibits an immune response remarkably similar to a patient with sepsis (8, 14). It appears that the initial tissue damage and hypo-perfusion associated with shock is linked to the inflammatory response in a circular pattern. Tissue damage and shock leads to inflammation, which, if of a significant magnitude, leads to more tissue damage and shock (64). Current concepts of resuscitation are aimed at breaking this cycle thus allowing a more physiologic resolution of the inflammatory response, hopefully avoiding later detrimental sequelae (60).

Hypoperfusion of the microcirculation with traumatic shock causes the normal hemostasis of the vascular endothelium to be disrupted (Figure 3) (15-17). The normally quiescent endothelial cells are denuded of the covering glycocalyx (61, 62, 65). This results in the loss of the molecular filtration function of the glycocalyx and also allows the endothelial adhesion molecules intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) to be exposed (66). Loss of this glycocalycal filtration along with disruption of the endothelial gap junctions allows the capillary leak that is typical of SIRS (67). Loss of intravascular proteins and volume to the tissue interstitium worsens tissue oxygenation and perfusion and is clinically evident as tissue edema (59, 60, 67). Elevated levels of glycocalyx degradation products have recently been correlated with mortality (57).
Exposure of the endothelial adhesion molecules is an important and necessary function of immunity in that leucocytes are activated and recruited to the site of infection and tissue damage (66). However, an inflammatory response of sufficient magnitude may cause systemic glycocalyx degradation, endothelial cell swelling and apoptosis and widespread tissue edema with a resultant impairment of microperfusion and tissue oxygenation (59-62, 64, 67). This is contributory to the lactic acidemia associated with worse outcomes (68, 69).

The initial hypo-perfusion and tissue damage associated with shock initiate an inflammatory response that may be modulated by appropriate fluid resuscitation while minimizing blood loss from sites of uncontrolled bleeding, an approach described as damage control resuscitation (DCR) (70). Permissive hypotension is typically one of the features of DCR in an attempt to prevent dislodging any fragile extravascular clots, as is limitation of crystalloid fluids (70). Somewhat in opposition to this therapy, current recommendations include maintenance of blood pressure in the setting of traumatic brain injury (71). Also, hypotensive, severely injured blunt trauma patients benefit from high fluid (>500ml) resuscitation in the field, unlike their normotensive counterparts (72). Indeed, guided crystalloid fluid resuscitation in the field improves outcomes (73). However, recent data associates greater than 1.5 liters of crystalloid resuscitation in the emergency department with increased mortality (74). Thus the question remains, what is the best resuscitation fluid to minimize the inflammatory complications of severe trauma? The patient's own blood would certainly be the best intravascular fluid to be administered (75). Indeed, the patient's own blood is perfectly immunologically matched, contains no risk of new exposure to infectious agents, contains components and mediators that are not commercially available, and typically does not contain elevated levels of storage damaged red blood cells. Also, there is no citrate or other exogenous anti-coagulant preservatives. Current resuscitation fluids fall short of these desired properties and transfused blood products carry considerable risks of their own (75-78). In fact, red blood cell administration is considered by many to be the most frequent “transplant procedure” performed worldwide. Transfusion initiated immune responses, although largely overshadowed by the massive response due to the traumatic injury itself, are significant (79). Fresh frozen plasma, especially the AB negative units included in a MTP protocol for blind use, carry significant risks for inflammation associated morbidity such as transfusion related acute lung injury (TRALI) and acute respiratory distress syndrome (ARDS), as well as transfusion associated circulatory overload (TACO) (13, 75, 80). Prompt administration of appropriate blood products to the correct subset of patients can significantly decrease the total blood product requirements (81). Thus, it is important to identify those patients likely to require a massive transfusion as early as possible (82). After identification, a pre-planned massive transfusion protocol should be initiated (11, 81, 82). The benefits of this protocol is multifold: 1) Prompt communication of the current critical blood product needs, 2) subsequent rapid acquisition of immediately necessary blood products, 3) blood bank notification of incoming blood samples for immediate cross match, 4) seamless integration of cross matched products as soon as available, 5) clinical lab notification of incoming STAT coagulation and other lab samples (83). A typical massive resuscitation begins with an initial limited crystalloid administration (72). This is quickly followed by early aggressive attempts to minimize and correct coagulation disorders and anemia (9, 11). Approaches to the acute resuscitation of
Coagulopathy are not uniform worldwide. Notably, there exists a dichotomy of approaches that are commonly referred to as the European and American strategies (84). Both utilize point of care coagulation testing such as thromboelastography (ROTEM and TEG); however, the European model promotes the use of specific concentrated pro-coagulant factor administration in contrast to the use of fresh frozen plasma and cryoprecipitate commonly used in the American model (84). Complications associated with FFP administration are cited in the European model as a reason for use of concentrated factors rather than FFP. Cryoprecipitate as well, is associated with significant morbidity. In the European model, concentrated fibrinogen is administered instead of cryoprecipitate. Though given typically to increase fibrinogen levels, cryoprecipitate has many other constituents including factor XIII and von Willebrand factor. These are likely beneficial in the setting of ACOT. Likewise, FFP contains more than just factors. There is current interest in the possibility that FFP may contribute to repair of the glyocalyx (9). If this in fact proves to be the case, it would help explain the decreased morbidity and mortality rates associated with increased FFP:RBC ratios (12, 85-87). It is a current topic for debate whether a goal of “whole blood” (1:1:1 PRBC:FFP:platelets or similar ratio) or a laboratory based, protocol driven approach of resuscitation utilizing patient specific pro-coagulant therapy is more efficacious. More research is needed to compare these two models.

Conclusion

In summary, therapeutic approaches for severe trauma, one of the leading causes of morbidity and mortality worldwide, have not really changed during the past thirty years despite a better understanding of the pathophysiology of trauma. In particular, new studies have shown that the inflammatory response to massive trauma is intrinsically linked to the activation of the coagulation cascade while many procoagulant factors induce a strong inflammatory response. Furthermore, there is also new evidence that the resolution of the inflammatory response is an active process, not a passive one. However, the recent introduction of the concept of damage control resuscitation may provide new avenues for decreasing the intensity of the inflammatory response while rapidly correcting coagulation abnormalities and hastening the repair of tissue damage associated with severe trauma. This approach includes a better choice of fluid for trauma resuscitation, a better control of blood loss from sites of uncontrolled bleeding, a better monitoring of the coagulation system by thromboelastography and of the severity of tissue hypoperfusion by measuring new mediators using a metabolomic approach. Finally, new prospective multicenter studies will be needed to demonstrate a survival advantage with damage control resuscitation in patients who have sustained a severe trauma.

Acknowledgments

The authors report that they have no conflicts of interest regarding this article.

Funding Support: NIH RO1 GM086416 (JFP)

References

1. WISQARS database [Internet].

Curr Opin Anaesthesiol. Author manuscript; available in PMC 2015 April 01.


9••. Peng Z, Pati S, Potter D, Brown R, Holcomb JB, Grill R, et al. Fresh frozen plasma lessens pulmonary endothelial inflammation and hyperpermeability after hemorrhagic shock and is associated with loss of syndecan 1. Shock. 2013; 40(3):195–202. This article helps to explain the most recently recognized benefit of fresh frozen plasma administration in a setting of hemorrhagic shock. Increased vascular permeability, inflammation, and systemic shedding of syndecan-1 due to glycocalyx damage are improved after fresh frozen plasma administration. This is likely associated with the improved survival noted with DCR. [PubMed: 23807246]


41•. Recchiuti A, Serhan CN. Pro-Resolving Lipid Mediators (SPMs) and Their Actions in Regulating miRNA in Novel Resolution Circuits in Inflammation. Frontiers in immunology. 2012; 3:298. This is a review of the active (not passive) nature of inflammation resolution. [PubMed: 23093949]


57. Johansson PI, Stensballe J, Rasmussen LS, Ostrowski SR. A high admission syndecan-1 level, a marker of endothelial glycosylation degradation, is associated with inflammation, protein C


63•. Cohen MJ. Towards hemostatic resuscitation: the changing understanding of acute traumatic biology, massive bleeding, and damage-control resuscitation. The Surgical clinics of North America. 2012; 92(4):877–91. viii. This paper reviews the history of resuscitation and points to our need to better understand inflammation and coagulation in order to continue to advance in this area. [PubMed: 22850152]


72•. Brown JB, Cohen MJ, Minei JP, Maier RV, West MA, Billiar TR, et al. Goal-directed resuscitation in the prehospital setting: a propensity-adjusted analysis. The journal of trauma and acute care surgery. 2013; 74(5):1207–12. discussion 12-4. This paper helps to clarify which patients benefit from pre-hospital crystalloid infusion. Severely injured blunt trauma patients not suffering from hypotension have worse outcomes after a high crystalloid (>500ml) resuscitation, but hypotensive patients do not. Correction of pre-hospital hypotension with crystalloid infusion was associated with improved survival in this subset of patients. [PubMed: 23609269]


84. Schohl H, Schlamp CJ. Trauma Bleeding Management: The Concept of Goal-Directed Primary Care. Anesthesia and analgesia. 2013 This is an excellent review of the differences, benefits and drawbacks of goal-directed vs. ratio driven hemostatic resuscitation models. This shows the dichotomy of approach to treating traumatic hemorrhagic shock. This is an intriguing area of significant debate.


### Key points

- The inflammatory response to massive trauma is interlinked with the coagulation cascade.
- Resolution of the inflammatory response is an active process, not a passive one.
- Damage control resuscitation may decrease the intensity of the inflammatory response and allow healing to proceed more normally.
Figure 1. The impact of coagulation on inflammation and the impact of inflammation on coagulation
Coagulation triggers platelet activation and leads to P selectin and CD40 ligand expression on the platelet surface. Ischaemia leads to cell death and the release of histones and HMGB1, both of which augment inflammation. Inflammation in turn leads to tissue factor induction, leukocyte adhesion, thrombomodulin down regulation, and complement activation. Thus, coagulation increases inflammation that in turn increases coagulation. Adapted from (44).
Figure 2. The vicious cycle of tissue damage and inflammatory response
Tissue damage causes a local inflammatory response that may become more systemic. This systemic inflammation leads to endothelial damage at distant sites (including the lungs). The resulting tissue edema, decreased microperfusion and tissue hypoxia leads to more tissue damage.
Figure 3. Endothelial glycocalyx damage associated with systemic inflammation

The normal functions of the Endothelial Surface Layer (ESL) to maintain homeostasis are lost when glycocalyx degradation occurs. Loss of plasma proteins and fluid to the interstitium, inappropriate activation of coagulation and immune competent cells all contribute to edema and microcirculatory compromise.