REVIEW OF THE CURRENT KNOWLEDGE OF THE PATHOPHYSIOLOGY OF ACUTE TRAUMATIC COAGULOPATHY: IMPLICATIONS FOR CURRENT TRAUMA RESUSCITATION PRACTICES

by

Alghalya Al-Maawali

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Abstract

Background: Deaths from exsanguination following trauma remain a clinical challenge. Current massive transfusion protocols embrace empiric resuscitation with packed red blood cells, plasma and platelets in a set ratio. With the evolving knowledge about acute traumatic coagulopathy (ATC) as a major contributor to exsanguination related deaths, it is apparent that current resuscitation protocols may fail to address the early coagulation deficits in trauma.

Objective: To provide a review of the current literature related to the pathophysiology of ATC in order to guide clinicians in optimizing diagnostic and therapeutic strategies in massively bleeding trauma patients.

Methods: Online search from the Medline database of all published articles since 2003 till March 2014.

Results: Initial search resulted in 20,504 articles of which 54 were included. Principle findings include: (1) Activated protein C is strongly linked to ATC pathophysiology and related to shock and tissue injury. (2) FV is commonly depleted, but thrombin generation is preserved, potentially minimizing the role of FV in ATC. (3) Hypofibrinogenaemia occurs very early in trauma and is strongly associated with higher mortality. A lower threshold for administration of fibrinogen-containing products should therefore be considered. (4) Hyperfibrinolysis incidence is low but is associated with increased transfusion requirements and higher mortality. Fibrinolytic activation is evident in almost half of trauma patients and is associated with higher injury severity score and higher mortality compared to patients with no fibrinolytic activation. (5) Platelet dysfunction plays a more important role in ATC pathophysiology compared to platelet counts. (6) Endothelial damage and sympathoadrenal activation are associated with glycocalyx degradation, higher adrenaline levels and autoheparinization, all contributing to the bleeding diathesis in trauma.

Conclusion: ATC is a complex endogenous state of hypo-coaguloability in shocked and severely injured trauma patients and is associated with increased transfusion requirements and higher mortality. Early fibrinogen depletion and fibrinolysis appears to play a central role in ATC and modification of current empiric resuscitation protocols in order to address these hemostatic deficits is needed. New knowledge of ATC is rapidly expanding, requiring regular reviews and knowledge dissemination to inform clinicians and guide appropriate management of ATC.
Preface

- The inception of this dissertation was a collaborative process involving Dr. Richard Simons, Dr. Daniel Frith and Dr. Alghalya Almaawali. I (AA) was the principle investigator and my responsibilities started with searching for published studies in the search engines and filtering relevant papers that met the inclusion and exclusion criteria. Under the supervision of Dr. Simons and Dr. Frith I selected the most recent and relevant studies that addressed the main question. I formatted all the studies into tables for comparison and summarized the collated results. An expert discussion panel was conducted including: Dr. Richard Simons, Dr. Daniel Frith and Dr. Tyler Smith to study the implications of the study’s findings as addressed in chapter 4.

- A review paper summarizing the results from this thesis is being prepared at the current time. Alghalya Almaawali is principle author in collaboration with Dr. Frith and Dr. Simons. Manuscript should be ready for submission at the same time as this thesis.

- Some of the data used in Chapter 3, reference (24) by Davenport et al. is currently unpublished and permission to use was given by Dr. Frith, a co-author.
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<tr>
<td>TIC</td>
<td>Trauma induced coagulopathy</td>
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<tr>
<td>ATC</td>
<td>Acute traumatic coagulopathy</td>
</tr>
<tr>
<td>ECT</td>
<td>Early coagulopathy of trauma</td>
</tr>
<tr>
<td>ACoTS</td>
<td>Acute coagulopathy of trauma shock</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency department</td>
</tr>
<tr>
<td>INR</td>
<td>International normalized ratio</td>
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<tr>
<td>PTr</td>
<td>Prothrombin time ratio</td>
</tr>
<tr>
<td>PT</td>
<td>Prothrombin time</td>
</tr>
<tr>
<td>aPTT</td>
<td>Activated partial thromboplastin time</td>
</tr>
<tr>
<td>ISS</td>
<td>Injury severity score</td>
</tr>
<tr>
<td>BD</td>
<td>Base deficit</td>
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<tr>
<td>CCT</td>
<td>Conventional coagulation tests</td>
</tr>
<tr>
<td>TT</td>
<td>Thrombin time</td>
</tr>
<tr>
<td>TEG</td>
<td>Thrombelastography</td>
</tr>
<tr>
<td>ROTEM</td>
<td>Rotational thromboelastometry</td>
</tr>
<tr>
<td>rTEG</td>
<td>Rapid thrombelastography</td>
</tr>
<tr>
<td>R</td>
<td>Reaction time</td>
</tr>
<tr>
<td>K</td>
<td>Kinetics</td>
</tr>
<tr>
<td>MA</td>
<td>Maximum amplitude</td>
</tr>
<tr>
<td>CL</td>
<td>Clot lysis</td>
</tr>
<tr>
<td>CT</td>
<td>Clotting time</td>
</tr>
<tr>
<td>CFT</td>
<td>Clot formation time</td>
</tr>
<tr>
<td>MCF</td>
<td>Maximum clot firmness</td>
</tr>
<tr>
<td>LY</td>
<td>Clot lysis</td>
</tr>
<tr>
<td>ADP</td>
<td>Adenosine diphosphate</td>
</tr>
<tr>
<td>vWF</td>
<td>Von willebrand factor</td>
</tr>
<tr>
<td>TF</td>
<td>Tissue factor</td>
</tr>
<tr>
<td>TFPI</td>
<td>Tissue factor pathway inhibitor</td>
</tr>
<tr>
<td>PC</td>
<td>Protein C</td>
</tr>
<tr>
<td>aPC</td>
<td>Activated protein C</td>
</tr>
<tr>
<td>PAI</td>
<td>Plasminogen activator inhibitor</td>
</tr>
<tr>
<td>tPA</td>
<td>Tissue plasminogen activator</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
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</tr>
<tr>
<td>FDP</td>
<td>Fibrin degradation products</td>
</tr>
<tr>
<td>PAP</td>
<td>Plasmin-antiplasmin complex</td>
</tr>
<tr>
<td>EPL</td>
<td>Estimated percent lysis</td>
</tr>
<tr>
<td>MEA</td>
<td>Multiple electrode aggregometry</td>
</tr>
<tr>
<td>LTA</td>
<td>Light transmittance aggregometry</td>
</tr>
<tr>
<td>PRBC</td>
<td>Packed red blood cells</td>
</tr>
<tr>
<td>FFP</td>
<td>Fresh frozen plasma</td>
</tr>
<tr>
<td>Cryo</td>
<td>Cryoprecipitate</td>
</tr>
<tr>
<td>PCC</td>
<td>Prothrombin complex concentrate</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>AT</td>
<td>Antithrombin</td>
</tr>
<tr>
<td>GCS</td>
<td>Glasgow coma scale</td>
</tr>
<tr>
<td>TF</td>
<td>Transient fibrinolysis</td>
</tr>
<tr>
<td>TRAP</td>
<td>Thrombin receptor activating peptide</td>
</tr>
<tr>
<td>AA</td>
<td>Arachidonic acid</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>TXA</td>
<td>Tranexamic acid</td>
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I would like to start with special thanks to my supervisor Dr. Richard Simons for his continuous support and endless effort in supervising my thesis. His close supervision, guidance and inspiration were asset to my dissertation. His wisdom and humble personality made my master degree a very pleasant journey with unforgettable memories.

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Chapter 1 . Introduction

1.1 Background:

Trauma is considered a public health problem worldwide. Injury causes the death of approximately 5.8 million people each year, which accounts for 10% of the world’s deaths (1). More than 200,000 Canadians get hospitalized and approximately 13,000 die each year due to acute injury in Canada (2). Deaths due to trauma usually result from either central nervous system (CNS) related injuries or severe bleeding. While CNS related deaths are difficult to treat, deaths due to exsanguination and associated hypoxia, severe tissue injury and coagulopathy are treatable and represents the number one cause of preventable death after injury. Kreis et al. studied preventable trauma deaths and reported that up to 21% of non-CNS deaths are preventable (3).

Ongoing bleeding in trauma patients may be surgical (i.e. amenable to surgical maneuvers such as a suture) or non-surgical. Non-surgical bleeding from the small vessels, surgical incision sites and venipuncture sites are usually caused by a hemostatic derangement referred to as ‘trauma induced coagulopathy’ (TIC), a condition where the blood does not clot effectively. This bleeding cannot generally be controlled surgically with compression or putting a stitch though the vessel, but requires correction of the coagulopathy to enable intrinsic cessation of bleeding.

TIC was previously thought to be completely iatrogenic and a consequence of resuscitation in the acute trauma setting in which infusing resuscitation fluids and packed red blood cells to bleeding patients results in hemodilution of clotting factors and platelets. In addition, hemostatic measures will be affected by the add-on effect of hypothermia, acidosis and ongoing inflammation. The endogenous component of TIC was only recognized recently when multiple studies reported the presence of the coagulopathic disturbance on the scene and before arrival to the hospital. This endogenous component of TIC is referred to as ‘acute traumatic coagulopathy’ (ATC), which is the focus of this review.

1.2 Acute traumatic coagulopathy’s impact on trauma patient outcomes:

Coagulopathy in trauma has become one of the most active areas of research in trauma recently. This is mainly due to the negative impact of coagulopathy on clinical outcomes. So far, all reported epidemiological studies addressing ATC have shown that it increases mortality by 4- to 6-fold and increases transfusion requirements (4,5,6,15). Putatively, ATC exacerbates blood loss by diminishing the bodies’ ability to maintain vascular integrity. Further, derangement of coagulation networks is strongly associated with hyper-inflammatory states and subsequent induction of multi-organ failure (MOF). In the recent study published by Cohen et al, they reported that patients with ATC had greater transfusion requirements, more ventilator days, higher preponderance of multi-organ failure and significantly higher in-hospital mortality (4). In addition, other studies demonstrated that coagulopathic hemorrhage is strongly associated with
posttraumatic mortality in the first 24 hours (7,8). The idea that this outcome could be impacted favorably if the coagulopathy was prevented or effectively treated makes ATC a topic of significant scientific interest.

1.3 Incidence of ATC:

Studies showed that ATC starts on scene and before the initiation of fluid resuscitation. It’s often present on patient arrival in the emergency department (ED). In 2003, Brohi et al. studied 1088 patients who received minimal fluid resuscitation in the field and they found that significant coagulopathy was present in 24.4% of patients on arrival in the ED (9). Subsequently several additional studies confirmed that coagulopathy was already present on scene and/or upon arrival to the emergency department (4,5,6,10,11,12). Incidence of ATC was reported in a wide range of 9% to 56% of trauma patients. This wide range in incidence is likely explained by the heterogeneity of the trauma patient cohorts studied and the different definitions of coagulopathy. In fact, different groups proposed a variety of definitions of coagulopathy in trauma and the laboratory methods used to detect it, which is a separate large area of research by itself.

1.4 ATC definition:

ATC is a state of hemostatic disturbance with multiple physiological activations and inhibitions that is evident on trauma scene. These hemostatic changes are worsened by the additional physiological challenges of hypothermia, acidosis and hemodilution that may be coincident at presentation or develop following hospital arrival due to suboptimal resuscitation protocols and practices. The risk of developing this condition is increased with increasing severity of tissue injury, lower blood pressures, higher base deficits and severe head injuries (22,38) and is associated with very high mortality.

Various definitions have been proposed to define coagulopathy in trauma patients in the literature. Hess et al. studied the prevalence of abnormal conventional coagulation tests in trauma population and reported results from 15,728 trauma patients (15). He found an increased risk of mortality in trauma patients presenting with an INR higher than or equal to 1.3 and injury severity score more than 15. Frith et al. proposed a similar value to Hess and defined acute traumatic coagulopathy as having a PTr/INR greater than1.2 (13). In Frith’s study, trauma patients with $PTr \geq 1.2$ had a greater transfusion requirements and higher mortality rates. Moreover, other investigators used an INR value of greater than or equal to 1.5 as an abnormal coagulopathy in trauma patients, and it was also associated with higher transfusion requirements and higher mortality (5,10). The definite numerical definition of acute traumatic coagulopathy has been debated, and with the new developing knowledge and new proposed diagnostic measures this debate is expanding.

1.5 Drivers of ATC:

An appreciation of the initiators and drivers of hemostasis in trauma is required to be able to understand the pathophysiology of ATC. This understanding is crucial as it informs the treatment options in the clinical setting. It is now clear that the
Hemostatic changes in trauma are initiated by both severe tissue injury and systemic hypoperfusion. In 2010, a multivariate analysis of 1987 patients from the German registry conducted by Wafaisade et al. concluded that acute traumatic coagulopathy is initiated by severe tissue injury and driven by on-going shock status (11). They reported that coagulopathy was not evident in trauma patients with tissue injury without shock, or vice versa. Furthermore, Frith et al. reported similar results in the same year (13). They reported that in over 5000 trauma patients from five different international centers, clinical coagulopathy was only evident with a combined increase in injury severity scores (ISS) and base deficit (BD). The findings of this clinical study were corroborated in a rat model of ATC. Again, significant coagulopathy was only evident in the animals subjected to both trauma and hemorrhagic shock. These studies and a few more (6,10,12,14,15) proved that TIC has an endogenous component that presents very early in trauma. These endogenous changes, referred to as ATC, are exacerbated by acidosis, hypothermia and hemodilution, which develop over time and account for the overall TIC.

Figure 1.5.1 Trauma Induced Coagulopathy. (73)

1.6 Diagnostic measures of ATC:

Most trauma centers screen all of their patients with the following tests: complete blood counts, urea and electrolyte, arterial blood gasses, INR, aPTT, fibrinogen levels and D-dimer. Conventional coagulation tests (CCT); INR and aPTT are
currently used as standard for diagnosing coagulopathy in trauma patients. Fibrinogen levels and D-dimer levels are also used in some centers as a guide of remaining fibrinogen level and coagulation factor consumption. The obtained results should provide a guide for the resuscitation needed. But, in severely injured trauma patients, resuscitation usually starts before any laboratory results are available and is usually guided by an empirical formula of blood products, especially in cases of exsanguinating hemorrhage. By the time the CCT results are available, the patient will be in a more advanced picture of coagulopathic disturbance and resuscitation products suggested by these results may no longer be relevant.

The utility of detecting trauma-induced coagulopathy by these CCT is debatable. These tests were initially used for the diagnosis of blood disorders like hemophilia and then later adapted for anticoagulant drug monitoring (47). The normal values were obtained from the general population and experts in the trauma and transfusion medicine field doubt its applicability in the trauma population. In addition to the long laboratory times required for CCT results, these test don’t entirely address the complexity of ATC. They provide no information about hyperfibrinolysis and clot strength, which are major components of ATC, thus provide an incomplete picture of the transfusion requirements or the need for administration of anti-fibrinolytic agents.

As a result, several new studies of ATC employed point-of-care, whole-blood-viscoelastic assays (e.g. TEG: thrombelastography, ROTEM: rotational thromboelastometry). These assays were able to provide faster results when compared to the CCT and were more useful in guiding resuscitation therapy as they better captured the various components of ATC (16,17,18,19) except for endothelial damage. Holcomb et al. investigated the ability of replacing CCT with rapid thrombelastography (rTEG) in 1974 patients (18). They concluded that taken together the speed, cost-benefit, functional information obtained and decreased amount of blood required to run the test, admission rTEG can replace CCT in assessing ATC. Even though these devices are supporting the developing understanding of the various complex changes in trauma hemostasis, results from randomized control trials confirming the efficacy of whole-blood viscoelastic tests in providing individualized hemostatic management to trauma patients are still lacking, though such studies are underway. As a result TEG® and ROTEM® have yet to achieve mainstream clinical application and trauma transfusion practices remain empiric for the most part.

1.7 Background about TEG and ROTEM in trauma:

TEG and ROTEM are both considered as real-time measures of the viscoelastic properties of clot formation and dissolution. They describe the process of clot initiation, strength and breakdown in whole blood or citrated blood and display results in a single graph. In addition, they provide information about thrombin generation, fibrinogen’s and platelets’ relative contributions to clot formation, clotting factor deficiencies and rate of fibrinolysis.

Performing the test requires collecting a small blood sample from the patient into the test cup. A pin is suspended in the cup that is connected to a detector system.
The detector system is a torsion wire in TEG machine and an optical detector in ROTEM machine. The pin and the cup rotate relative to each other at an angle of $4^\circ 45'$ to activate the coagulation. In TEG the cup initiates the movement while it’s initiated by the pin in ROTEM device. The speed at which the blood clot forms and subsequently dissolves reflects the efficacy of the blood’s coagulation factors, platelet function and fibrinolytic activity. Additional information about the patient’s blood hemostatic condition could be obtained by the changes in the clot strength and elasticity.

The difference between these viscoelastic assays and the CCT is that they provide a global picture of the patient’s hemostatic and fibrinolytic activity. They were initially mainly used in liver transplantation and cardiac surgery until recently when their use in trauma coagulopathy was proposed (17, 19). Their use as a point-of-care practice in trauma is attractive as they provide more detailed information about how TIC begins and progression of the coagulopathy after trauma.

Viscoelastic whole blood assays reflect all three stages of hemostasis: initiation, amplification and propagation. All results of the different phases get formulated into one graph (Figure 1.7.1).

Figure 1.7.1 TEG® and ROTEM® tracing

![TEG® and ROTEM® tracing](image)

* TEG® and ROTEM® tracing TEG® parameters: R – reaction time; k – kinetics; $\alpha$ - alpha angle; MA – maximum amplitude; CL – clot lysis. ROTEM® parameters: CT – clotting time; CFT – clot formation time; $\alpha$ - alpha angle; MCF – maximum clot firmness; LY – clot lysis (48).

1.7.1 Nomenclature of TEG and ROTEM:

Clot time is referred to the time from the start of the reaction until 2 mm amplitude of clot formation. This is referred to as R (reaction time) in TEG and CT (clotting time) in ROTEM. Clot kinetics are usually represented by two values; the first is the time period from 2mm to 20 mm clot amplitude, K (kinetics) in TEG and CFT (clot formation time) in ROTEM, and the second is alpha angle, which represents the slope between R and K in TEG and the slope
tangent at 2mm amplitude in ROTEM. Clot strength is also represented by two values, MA (maximum amplitude) and G (clot elasticity) in TEG, and MCF (maximum clot firmness) and MCE (maximum clot elasticity) in ROTEM, representing maximum strength and clot elasticity respectively. G and MCE are computer-generated values that reflect the overall clot strength from initial fibrin formation to fibrinolysis. Finally clot lysis is measured at fixed times; in TEG, amplitude reduction in 30 and 60 minutes after MA is referred to as Ly30 and Ly60 respectively, in ROTEM, it's referred to as CL30 and CL60 (clot lysis) (49).

1.7.2 Results interpretation (using TEG® nomenclature):

- High R-value: prolonged clotting time; indicates clotting factors dysfunction; either to loss, consumption or dilution.
- High K-value: indicates a state of hypofibrinogenemia.
- Low alpha angle: indicates hypofibrinogenemia or platelet dysfunction.
- Low MA: indicates hypofibrinogenemia or platelet dysfunction.
- Low G value: indicates a hypocoagulable state. G value represents a global measure of clot strength and reflects both, enzymatic and platelet dysfunction.
- High Ly30; indicates increase fibrinolytic activity.

These results aim to guide the transfusion requirements resulting in an individualized goal directed therapy.

1.8 Hemostasis background:

Hemostasis is a physiological process that occurs in response to vessel injury characterized by a balanced dynamic between clot formation (by fibrin generation) and clot lysis and tissue remodeling (plasmin induced fibrinolysis). Hemostasis can be divided into four different phases; initiation and platelet plug formation, propagation by clotting cascade, termination of clot formation and finally clot elimination and fibrinolysis. It’s important to keep in mind that these phases are interacting and overlapping, and the separation is made to facilitate understanding the complex process. The overall coagulation picture in a patient depends on which of these processes predominate at any given time (clot generation vs. lysis) (50).

1.8.1 Initiation and platelets plug formation:

In the initial phase, platelets play a major role as the primary soldier of hemostasis. Platelet plug formation could be divided into the following: adhesion, aggregation, platelet secretion and procoagulant activation. Once the endothelium is injured, the subendothelial collagen gets exposed and in addition to circulating ADP, thrombin and epinephrine, it activates platelets. Platelet activation results in shape change to a more adhesive form where, in the presence of vWF, it binds to collagen. In addition, once platelets are activated the GPIIb/IIIa receptors become exposed and aggregation phase commences. The exposure of these receptors lead to conformational changes resulting in high affinity to fibrinogen and binding to platelet cytoskeleton.
The latter process results in clot retraction and platelet spreading. After that, platelets secrete different molecules from its alpha and dense granules resulting in more activation, aggregation, vasoconstriction and stability of the platelet plug. Finally, on the surface of these platelets, enzymes complexes needed in the clotting cascade get assembled. This assembly occurs in response to the exposure of procoagulant phospholipids at the platelet surface, and from here the second phase of hemostasis starts.

1.8.2 Propagation by clotting cascades:
This phase could be defined as a multiple activations of pro-enzymes to active enzymes leading to stepwise response amplification. Multiple component macromolecular complexes facilitate the function of these enzymes, resulting in faster and more efficient enzymatic reactions. Historically, clotting cascade has been divided into extrinsic pathway, intrinsic pathway and common pathway. The extrinsic pathway gets activated by released tissue factor (TF) and measured by prothrombin time (PT). The intrinsic pathway gets activated by negatively charged surfaces and measured by activated partial thromboplastin time (aPTT). Both pathways converge at the activation of factor X that converts prothrombin (factor II) into thrombin (the last enzyme in the clotting cascade).

Dividing clotting cascade into intrinsic and extrinsic pathways, though helpful in laboratory interpretations, is not entirely physiologically accurate. It has become clear that there are two phases of thrombin generation. First, the initiation of thrombin; mediated by TF and VIIa which result in small amounts of thrombin through factor X activation. Second, amplification or thrombin burst formation through the activation of factors V, VIII, XI and platelets by the initially formed thrombin. Once thrombin is formed, it converts soluble fibrinogen into insoluble fibrin, which then gets stabilized through cross-linking by activated factor XIII (50).

As mentioned above, the function of these enzymes is facilitated by multiple component macromolecular complexes. Examples of these complexes are:

- Extrinsic X-ase (VIIa+TF+X)
- Intrinsic X-ase (IXa+VIIIa+X)
- Prothrombinase (Xa+Va+prothrombin)
- The protein C anticoagulant complex (thrombin+thrombomodulin+protein C)

1.8.3 Termination of clot formation:
The formation of platelet plug and the interaction with clotting cascade results in a fast and localized hemostatic response. This response should be checked and controlled otherwise it might result in a systemic generalized thrombosis. Dilutional effect of clotting factors in the flowing blood, catabolism of different procoagulants in the liver and natural antithrombotic pathways are methods used to terminate the clot formation. In addition to these methods, prostacyclin/thromboxane/nitric oxide also plays a role in the termination of clot formation.

Natural antithrombotic pathways are: Antithrombin (AT) pathway, Protein C pathway and Tissue factor Pathway Inhibitor (TFPI).
• AT pathway; antithrombin works by neutralizing most of the clotting cascade enzymes by forming irreversible complexes. It also binds to heparin through specific heparin receptors to facilitate this pathway.

• Activated Protein C Pathway: Thrombin binds to soluble thrombomodulin forming thrombin-thrombomodulin complex, this complex uses protein C as a substrate and converts it into activated protein C (aPC). Via cofactor PS, aPC degrades factors V and VIII. In addition, the bonding between thrombin and thrombomodulin causes conformational changes in thrombin. As a result, the new thrombin cannot activate more platelets and loses its ability to cleave fibrinogen.

• TFPI; Tissue factor pathway inhibitor is a plasma circulating enzyme that works by inhibiting thrombin generation either by deactivating factor X through binding to it, or inhibiting TF/VIIa through TFPI/Xa complex.

1.8.4 Clot dissolution and fibrinolysis:
Clots need to be organized and broken down in order to restore blood flow in injured vessels. At this stage, plasminogen binds to fibrin and is converted to plasmin by tPA (tissue plasminogen activator). Plasmin is responsible for breaking down fibrin, fibrinogen and many other plasma proteins and clotting factors. Fibrin degradation products (FDP; e.g. D-dimer) are the result of fibrinolysis. This whole process is complex and balanced by plasmin inhibition (by alpha-2-antiplasmin) and tPA inhibition (by plasminogen activator inhibitors 1 and 2). In addition, thrombin-thrombomodulin complex activates thrombin activatable fibrinolysis inhibitor TAFI that slows down the clot lysis.

1.9 Background of ATC pathophysiology:
The actual pathophysiology behind acute coagulopathy in trauma patients is yet to be fully defined. Current evidence indicates that it’s a disturbance in the equilibrium of hemostasis components. ATC cannot be defined as a change in the INR measure alone, or low platelet counts or even changes in fibrinogen levels. It is one large umbrella with combined changes in each component of hemostasis that includes changes in the procoagulant factors, changes in systemic anticoagulation, changes in platelet counts and activation, hyperfibrinolysis, endothelial damage and sympathoadrenal activation. These changes have been addressed both separately and in combination in the literature.

1.9.1 aPC in ATC: The synergistic effect of severe tissue injury and shock has been associated with systemic anticoagulation through the activation of protein C pathway. Thrombin-thrombomodulin complex activate protein C that leads to enhanced systemic anticoagulation. aPC affects hemostasis by 2 main actions. Firsts, aPC result in deactivation of FV and FVIII, disturbing the thrombin generation. Second, it promotes fibrinolysis by consuming PAI-1 and resulting in more available tPA.
1.9.2 **Fibrinogen in ATC:** Fibrinogen plays a major role in the clot formation and is the key substrate that normal hemostasis is dependent on. It is increasingly recognized that fibrinogen levels are reduced in severely injured trauma patients and is related to increased mortality and morbidity (31). The most clinically relevant level of decreased fibrinogen in trauma patients is still unclear and yet to be defined.

1.9.3 **Hyperfibrinolysis in ATC:** Hyperfibrinolysis refers to an enhanced fibrin breakdown process and has been identified as a component of ATC in trauma patients and associated with lethal non-surgical hemorrhage (27,37). The detection of such a process is usually measured by the levels of fibrin degradation products e.g. D-dimer, or by measuring the plasmin-antiplasmin complex PAP. The conventional coagulation tests like INR/PT and aPTT do not assess fibrinolytic activity. On the other hand, viscoelastic whole blood assays like TEG are more sensitive and define hyperfibrinolysis as LY30 >7.5% (clot lysis at 30 minutes from maximum amplitude greater than 7.5) or EPL >15% (estimated percent lysis). LY30 and EPL are both used to estimate the reduction in clot strength (33).

1.9.4 **Platelets in ATC:** Platelet count has been routinely measured in trauma patients as an essential test in most, if not all, trauma centers. But, recent studies are suggesting that platelet (dys)function plays a more integral part in the coagulation disturbance in trauma patients compared to platelet counts. In trauma, Multiple Electrode Aggregometry (MEA) assays and TEG platelet mapping are new suggested methods for platelet function measurements. Both methods demonstrated good correlation to the Light Transmission Aggregometry (LTA) test, which is the gold standard test for platelet function assessment (74,75,76). LTA use in trauma is not feasible considering it is very time consuming and requires intensive labor.

1.9.5 **Endothelial damage and sympathoadrenal activation:** The role of endothelial damage, inflammation and sympathoadrenal activation form a huge bulk of the expanding knowledge in ATC pathophysiology. Intensive research is being conducted to try to understand the complex process of hemostatic changes that occur after trauma. Evidence so far suggests a role of glycocalyx degradation and autoheparinization.

1.10 **Massive transfusion in trauma:**

Massive transfusion is the administration of different blood products to patients in response to uncontrolled bleeding with ongoing losses. It is historically defined as the transfusion of more than or equal to 10 units of Packed Red Blood Cells (PRBC) in 24hours. Other, more recent, definitions include transfusion of 6 units or more of PRBC in one bleeding episodes with ongoing losses or transfusion of 4 or more units of PRBC in 1 hour with ongoing losses. In response to ongoing bleeding in trauma, the resuscitating physician is responsible for choosing what
blood components to give taking into consideration restoration of intravascular volume state, proper tissue oxygenation and management of the hemostatic and metabolic changes that the bleeding patient experiences. Following initial resuscitation with crystalloid fluids, early use of blood products/components such as PRBC, Fresh Frozen Plasma (FFP), Platelet Concentrates, Cryoprecipitate (Cryo), Prothrombin Complex Concentrate (PCC) and fibrinogen is required in the resuscitation of bleeding trauma patients to achieve physiological recovery and correction of coagulopathy.

Each unit of FFP or thawed plasma (250ml approximately) contains all clotting factor in their normal concentration thawed from 1 unit of whole blood. It contains minimal red blood cells, platelets and leukocytes. Comparing FFP to Cryo, Cryo is prepared by controlled thawing of FFP. It constitutes only the high molecular weight proteins of the FFP (FVIII, vWF, Fibrinogen and FXIII). Both, FFP and Cryo can be stored frozen for up to 1 year and take about 25-30 minutes to be thawed. On the other hand, PCC contains the vitamin K dependent factors only; FII, IX, FX and a lesser amount of FVII (also proteins C and S) and requires no thawing.

Trauma practice guidelines differ for each trauma center in different parts of the world. Most guidelines will encourage transfusion of PRBC to reach a hemoglobin concentration target of 100 g/l after trauma. Transfusion protocols of FFP, Platelet concentrates and fibrinogen usage vary, but historically typically use cut-offs of INR>1.5, Platelet count <50 x 10⁹/L, or fibrinogen < 1.0 g/l, respectively (77,78). Thus, after initial resuscitation with crystalloid fluids and PRBC, transfusion of other components was only initiated if conventional coagulation and blood test results appeared to be abnormal. At the time this made sense because it was thought that coagulopathy in trauma is a result of clotting factors dilution (from fluid resuscitation) or loss (from bleeding). This practice necessarily resulted in delays in treating coagulopathies and under-recognition of those coagulopathies not identified with traditional CCT.

Recent studies have suggested that earlier and empiric administration of FFP and platelets with PRBC might improve patients’ outcomes. In a computer simulation study conducted by Hirshberg et al. they suggest that a concurrent transfusion of plasma with PRBC could prevent coagulopathy (51). Later, Ho et al. also suggested that giving more FFP and platelets early in resuscitation and before developing severe coagulopathy might improve survival in trauma patients (52). They recommended that resuscitation should be started early with a ratio of 1:1 for plasma, and to give a higher rate of 1-1.5 of FFP for each PRBC in patients with an established coagulopathic bleeding. Ganzolez et al. studied trauma patients’ coagulopathy who were massively transfused (more than or equal than 10 units of PRBC in 24h) (53). They looked at patients INR at admission to the emergency department and after being massively transfused, upon admission to the ICU (intensive care unit). Despite good management of hypothermia and acidosis, the used ratio of FFP: PRBC (total of 12 PRBC with 5 units of FFP, FFP is given only after the 6th unit of PRBC) was not sufficient to correct the coagulopathic disturbance. Patient admission INR was 1.8 +/- 0.2 compared to pre ICU INR 1.6 +/- 0.1). They recommended a more aggressive resuscitation with earlier and higher ratio of plasma.
The association between reduced mortality and the administration of a higher ratio of plasma was observed in several recent studies. In 2007, Borgman et al. data from 246 trauma patients admitted to US army combat hospital showed a strong association between plasma and PRBC ratio with survival (54). In their study, massively transfused trauma patients (10 or more PRBC in 24h) were retrospectively divided into 3 groups depending on the ratio of plasma given to PRBC units; low ratio (1:8), medium ratio (1:2.5) and high ratio (1:1.4). Patients in all groups had a similar median ISS of 18. Hemorrhagic mortality was found to be 92.5%, 78% and 37% in the three groups respectively.

After Borgman’s study, many trauma centers reviewed their data and most of the reported studies showed a similar association, which resulted in a clinical practice change. In 2008, Duchesen et al. questioned the practice in trauma resuscitation for the past 60 years (55). In his study of 135 patients who were massively transfused (10 or more PRBC in 24h) and required an emergency surgery, mortality was 87.5% in patients received 1:4 ratio of PRBC to plasma compared to 26 % in those received 1:1 ratio. He concluded that resuscitation with 1:1 ratio had a survival advantage. Three systematic reviews have been published investigating this association. Murad et al. showed that though the quality of evidence was weak, it was clear that plasma infusion at higher ratios was associated with a reduction in the risk of death and multi-organ failure (56). Johansson et al. (57) and Bhangu et al. (58) systematic reviews showed similar results. However, another association was noticed with giving higher ratios of plasma. Patients who received higher ratios found to have higher risks of developing acute lung injuries, a known risk factor of FFP (56). In addition, FFP transfusion carries the risk of transfusion immune mediated adverse reactions and the risk of viral transmission. There is also a high probability of survivor bias accounting for the apparent survival benefit to increased plasma ratios observed in many of these studies.

With the emerging use of new diagnostic tests in trauma for ATC (TEG/ROTEM), new available clotting factor concentrates (fibrinogen concentrates/PCC) and the well-recognized side effects of FFP, new resuscitation strategies are being proposed by a variety of authors worldwide. These new resuscitation strategies attempt to encompass the evolving new knowledge about ATC. An increasing body of evidence is showing that fibrinogen gets depleted early in trauma, a finding not appreciated until recently due to the limitations of standard CCT. Some have suggested giving fibrinogen early and before critical levels develop. Others suggested giving PCC as it is easily available and might carry fewer risks compared to FFP. Others suggested the use of goal directed therapy by TEG/ROTEM instead of 1:1:1 ratio. Different studies reported different results, and the best clinical practice cannot be defined till more randomized clinical trials (RCT) comparing each become available. What is increasingly apparent, however, is that ATC is a relatively common phenomenon, especially in the more severely injured and acidic patients, the nature of the coagulation deficits are heterogeneous and that resuscitation practices need to address these deficits in a timely fashion and be patient specific. The practice of waiting for standard CCT results to determine treatment, or using empiric formula driven protocols (e.g. 1:1:1) do not adequately address these issues and new strategies are required.
Though RCT comparing optimal resuscitation protocols in severely injured and shocked trauma patients are still lacking, some RCTs were published investigating other interventions in trauma resuscitation. The CONTROL trail investigated the use of recombinant FVIIa (rFVIIa) as a pro-coagulant in preventing hemorrhagic death in trauma (59). Patients were randomized into two groups where half received rFVIIa and half received a placebo. There was no difference in death prevention in both groups and hence there was no more role of rFVIIa in trauma resuscitation. Its worth to mention that this trial was terminated early due to lower mortality rates than expected. The CRASH-II trial investigated the use of tranexamic acid as an anti-hyperfibrinolytic drug in improving trauma patients’ survival (60). 20,211 trauma patients with increased risk of bleeding from 40 countries were enrolled. In the tranexamic acid group, overall mortality at 28days and death due to bleeding was significantly reduced. Hence, the use of tranexamic acid in trauma patients with risk of bleeding was recommended.

The wide variety of suggested resuscitation protocols and different interventions for trauma patients are related to the lack of knowledge of what is exactly being treated. In addition, rapidly evolving new knowledge in this field is published in a variety of clinical and non-clinical specialty journals, making it extremely for the busy clinician to stay current and tailor resuscitation practices accordingly. Current resuscitation protocols, therefore, are usually blunt instruments applied indiscriminately to all at risk trauma patients, but not patient tailored. With frequent analysis and compilation of the evolving knowledge of ATC and the pathophysiology underlying it as presented in this thesis and related publication, it is hoped that better resuscitation practices focused on identifying and replacing actual deficits and providing the support that the body actually needs can be achieved in the near future.

1.11 Aim

The aim of this thesis is to identify the incidence and nature of the different hemostatic abnormalities associated with ATC. This will be achieved by means of a systematic literature review and the knowledge obtained will serve a better understanding of the complex pathophysiology behind ATC. It’s expected that with such understanding more effective and patient-tailored resuscitation protocols will be proposed that can better address ATC and ameliorate the morbidity and mortality caused by it.
Chapter 2. Methods

Relevant articles and studies addressing the nature and frequency of coagulopathy following trauma (primary question) were identified from searches of Medline, PubMed, Embase, UBC library, ScienceDirect and The Cochrane library (2003-15 March 2014). Searches of the databases were additionally amplified by checking the reference lists of studies identified and of relevant papers. The following restrictions were applied: adult age group, published in 2003 or after, published in English, no reviews and no animal or lab studies. Studies published before the year 2003 were excluded, since trauma induced coagulopathy as a new concept was only introduced after Brohi et al. study in 2003 (9). Studies published addressing pediatric traumas, burns, traumatic brain injury as a main focus were excluded since the clinical management of these groups is different from the general trauma population. Studies published about lab simulation and/or experiments on animals were excluded because these didn't reflect our main intention of addressing the problem in the human clinical setting. Articles and studies about the trauma management and massive transfusion protocols that didn't address the nature or type of coagulopathy were also excluded. Only studies, which addressed coagulopathy on scene or upon admission to the emergency room, were included.


2.1 Data collection and analysis:
Titles and abstracts were screened for relevance to the mentioned criteria by the primary author. All the related articles that met the inclusion criteria were included at this stage and only clearly irrelevant articles were excluded. The abstracts of the selected studies were then reviewed in collaboration with supervising faculty and further exclusions were made on the basis of the defined inclusion and exclusion criteria and the relevance of the article in answering the primary question. Agreed on articles were then analyzed and the details abstracted from each were: study sample, study cohort (mean injury severity score ISS, mean Glasgow coma scale GCS, mean age, percentage of male gender, percentage of penetrating or blunt injury), definition of trauma induced coagulopathy, mean time to the emergency room, clotting factors levels, fibrinogen levels, platelets activity, platelets counts, hyperfibrinolysis incidence, activation of systemic anticoagulants, endothelial damage and sympathoadrenal activation and outcome.

The analysis was organized in tables by specific coagulation abnormalities and incidence of each abnormality (when available) was reported to facilitate the expert discussion panel in answering our primary question.
Chapter 3. Results

The initial search resulted in 20,504 articles, out of these, 235 were potentially relevant. After screening of title and abstract, 84 articles were included for full text retrieval. 30 articles were then excluded after full text review for not meeting our inclusion criteria or not answering our primary question. 54 articles were eventually included in this review.

Abnormalities in the different coagulation pathways are reported separately in an attempt to simplify the complexity of ATC and identify the relative frequency and importance of each component. The results are divided into the following sections: 1. Protein C pathway and ATC, 2. Procoagulants pathway in ATC, 3. Fibrinogen deficiency in ATC, 4. Hyperfibrinolysis in ATC, 5. Platelet abnormalities in ATC and finally 6. Endothelial damage and sympathoadrenal activity in ATC. The procoagulants in ATC are divided into 2 subsections; tissue factor and thrombin generation, and clotting factor abnormalities. Although fibrinogen is also considered a procoagulant, it was discussed separately considering its major role in ATC and the large number of studies found addressing its incidence.

3.1 Anticoagulants in ATC:

- **3.1.1 Protein C pathway:**
  
The search resulted in 6 studies supporting the idea of activated protein C pathway as a central component of acute traumatic coagulopathy. Brohi et al. showed that in trauma patients, increasing hypoperfusion was associated with high soluble thrombomodulin and low protein C levels (22). In addition, reduced protein C levels were associated with lower levels of plasminogen activator inhibitor-1 and high D-dimer levels. Johansson et al. reported similar results (23). Floccard et al. also reported similar results of decreased residual protein C activity in coagulopathic trauma patients in 2010 (12). More recent studies aimed to measure activated protein C levels and study its association with protein C activity and coagulopathy. Cohen et al. study of 1198 trauma patients (4) showed that elevated injury severity score and a high base deficit were significantly associated with higher levels of activated protein C. This finding was recently emphasized by Davenport et al. who linked the reduction in protein C activity with high levels of activated protein C (aPC<=3ng/ml: PC activity 91% vs. aPC >9ng/ml: PC activity 65%, p<0.001) (24). The same study showed that patients with ATC had 5 times higher levels of activated protein C when compared with patients with no coagulopathy. In addition, with increasing levels of activated protein C, Prothrombin Time ratio PTr increased and MCF (Maximum Clot Firmness) as measured by viscoelastic measures decreased.

- **3.1.2 Antithrombin pathway:**
  
  A reduction in antithrombin (AT) level in trauma patients was reported in few studies. In a study conducted by Dunbar and Chandler investigating ATC pathophysiology, they reported that coagulopathic patients had lower AT levels. Floccard et al. (12) and Cohen et al. reported that with increasing injury severity, AT levels go down.
3.2 Procoagulant pathway in ATC:

- **3.2.1 Clotting factor abnormalities and thrombin generation:***

Search of studies investigating clotting factor levels or activity in acute traumatic coagulopathy resulted in 8 studies. Findings are summarized in table 1. One of the major challenges was the heterogeneity of the study cohorts that made comparison difficult.

FV is reported to be depleted or to have reduced activity in all studies investigating clotting factor in ATC. This factor is special in that it is a target of activated protein C (aPC) cleavage and it is a cofactor in the common pathway required for thrombin generation. Factor V level and activity were reduced in 3 and 3 studies, respectively. Decreased levels of factor V below the normal range was a common finding in studies conducted by Cohen et al. (4), Shaz et al. (25) and Floccard et al. (12). In the study reported by Rizoli et al. investigating clotting factor deficiencies in early trauma coagulopathy, 20% of trauma patients had a critical deficiency of at least one clotting factor (46). Critical deficiency was defined as having a reduced activity of 30% or more and FV was commonly critically deficient in all of these patients. Similarly, Davenport et al (24) showed that FV activity is lowered in patients with ATC and/or elevated aPC.

In regards to FVIII, another factor targeted by aPC, levels were reported to be high in Jansen (26) and Davenport (24) studies, low in Rizoli (46) and Cohen (4) studies. Jansen et al. (26) reported that though factor V activity was decreased in 54% of patients, 72% of patients had high factor VIII activity. Jansen studied the effect of hypoperfusion in trauma patients on the overall activity of clotting factors, setting a normal range of a value between (0.5-1.5 U/ml). Similarly, Davenport reported that FVIII levels were found to be high in the ATC group, but FVIII:vWF was significantly reduced with increasing aPC indicating a relative inhibition of activated FVIII. On the other hand, FVIII was critically deficient in 4 out of 22 patients with CD in Rizoli study (46) and Cohen reported low FVIII among other factors (4).

In regards to the remaining CF, measurement of CF levels and activities were normal in the majority of the studies (24,26,12). Jansen et al reported that 76% of CF activity measurements in his trauma cohort were more than 0.5 U/ml (26). Similarly, Davenport et al showed that FII, FVII, FXI and FX activities were maintained above 80% (24). In addition, in Rizoli study, out of 22 patients who had CD, 77% (17/22) had a single deficiency (46). One study only reported a global reduction of CF in coagulopathic patients when compared to non-coagulopathic (4).

Other investigators used TEG/ROTEM in understanding the pathophysiology of acute traumatic coagulopathy. An abnormal clotting factor function is defined by an abnormal R-value (in TEG) or abnormal Clotting Time (in ROTEM). The search resulted in two studies that reported the incidence of having an abnormal R-value in their cohort study (27, 28). Both studies reported a similar incidence of abnormal clotting factor function up to approximately 60%. Even though R-value
does not specify which factors are exactly depleted, but it emphasizes the presence of an overall deficiency.

Interestingly, thrombin generation appears to be preserved in ATC. Most of the studies that investigated ATC pathophysiology reported increased prothrombin fragments 1+2 indicating an increase in thrombin generation. In a study performed by Dunbar and Chandler to investigate thrombin generation in trauma patients, they found that coagulopathic trauma patients had a higher thrombin generation (21). Furthermore, Brohi et al. data showed an association between injury severity and thrombin generation (22). Brohi reported that in 208 trauma patients, prothrombin fragments 1+2 increased with increasing injury severity scores. Shaz et al. data showed a similar evidence of increased thrombin generation in both of the study cohort (25).
Table 3.1: Clotting factors deficiencies incidence in trauma population

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Year</th>
<th>Study</th>
<th>Study sample</th>
<th>Cohort</th>
<th>Definition</th>
<th>Number/study sample</th>
<th>Incidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davenport (24)</td>
<td>2014</td>
<td>Activated protein C dependent fibrinolysis and fibrinogenolysis are central to acute traumatic coagulopathy.</td>
<td>300</td>
<td>ISS (10), ISS&gt;15 41%, age (33), 82% male, 21% penetrating</td>
<td>FV activity &lt;50%</td>
<td></td>
<td>85% of pt with ATC</td>
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<td></td>
<td>ATC = CA5&lt;=35mm</td>
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<td>FVIII:vWF ratio was significantly reduced with increasing aPC</td>
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<td></td>
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<td></td>
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<td>FVIII: increased activity</td>
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<td></td>
<td></td>
<td></td>
<td>FII,VII,IX,X: activity maintained at &gt;80%</td>
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<tr>
<td>Cohen (4)</td>
<td>2013</td>
<td>Clinical and mechanistic drivers of acute traumatic coagulopathy.</td>
<td>1198</td>
<td>ISS 26.2 +/- 15.3, GCS (14), 35.3% penetrating injury. Subset of 165 patients had CF analysis</td>
<td>ATC = INR &gt;=1.3</td>
<td></td>
<td>Low levels of FII,V,VII,VIII,IX,X</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>ATC = aPTT &gt;=35s</td>
<td></td>
<td>Low levels of FII,V,VII,VIII,IX</td>
<td></td>
</tr>
<tr>
<td>Rizoli (46)</td>
<td>2011</td>
<td>Clotting factors deficiencies in early Trauma-Associated coagulopathy.</td>
<td>101</td>
<td>Pt with CD: ISS (34), age (40.5), blunt 95.5%, male 22.7%. Pt with no CD: ISS (26), age (37), blunt 84.1%, male 27.3%</td>
<td>CD: Activity &lt;=30%</td>
<td></td>
<td>20%</td>
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<td>FV: 22/22</td>
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<td>FVIII: 100%</td>
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<td>FXI: 18%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>15%</td>
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<tr>
<td>Shaz (25)</td>
<td>2011</td>
<td>Pathophysiology of early trauma induced coagulopathy: emerging evidence for hemodilution and coagulation factor depletion.</td>
<td>383</td>
<td>ISS 14 +/- 13, blunt 77%. 38 patients with ATC chosen and matched with 53 control</td>
<td>ATC =Prolonged PT</td>
<td></td>
<td>Decreased levels of FV, FVII</td>
<td></td>
</tr>
<tr>
<td>Jansen (26)</td>
<td>2011</td>
<td>Hypoperfusion in severely injured trauma patients is associated with reduced coagulation factor activity.</td>
<td>71</td>
<td>ISS (29), age (32), male 77%, penetrating 13%, blunt/combined 87%,</td>
<td>Normal CF activity (0.5-1.5U/mL)</td>
<td></td>
<td>54%</td>
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<td>FV low activity 38/71</td>
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<td></td>
<td></td>
<td></td>
<td>FVIII high activity 51/71</td>
<td></td>
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<tr>
<td>Floccard (12)</td>
<td>2010</td>
<td>Early coagulopathy in trauma patients: an on-scene and hospital admission study.</td>
<td>45</td>
<td>ISS (25), ISS&gt;15 (33), age (32), blunt 100%, male 78%</td>
<td>ATC = (non-overt-TAC and overt TAC) by ISTH system</td>
<td></td>
<td>Only FV decreased with the severity of injury</td>
<td></td>
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<tr>
<td>Author</td>
<td>Year</td>
<td>Study</td>
<td>Study sample</td>
<td>Cohort</td>
<td>Definition</td>
<td>Number/study sample</td>
<td>Incidence</td>
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<td>Carroll (27)</td>
<td>2009</td>
<td>Early evaluation of acute traumatic coagulopathy by thrombelastography.</td>
<td>161</td>
<td>ISS (20), age (42), 73% male,</td>
<td>Abnormal R</td>
<td>93/161</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>Plotkin (28)</td>
<td>2007</td>
<td>A reduction in clot formation rate and strength assessed by thrombelastography is indicative of transfusion requirements in patients with penetrating injuries.</td>
<td>44</td>
<td>ISS (21+//-9.4), GCS (10+/5.6), BE (-5.8 +/- 5.2) 34% gun shot injury, 55% explosions injury</td>
<td>Abnormal R</td>
<td>26/44</td>
<td>59%</td>
<td></td>
</tr>
</tbody>
</table>

* Pt: patients, CD: Critical Deficiency, ATC: acute traumatic coagulopathy, TAC: trauma-associated coagulopathy, ISTH International Society on Thrombosis and Hemostasis, ISS: injury severity score, aPC: activated protein C.
3.3 Fibrinogen deficiency in ATC:

The search resulted in 6 studies that reported the frequency of abnormal fibrinogen level within their cohorts. All studies are summarized in table 2 with the documented frequency and incidence.

The various studies targeted different trauma populations and had different definitions of abnormal fibrinogen levels ranging from <0.8 to <2.0g/L, making comparison and summary difficult. The following points, however were clear and common among the studies.

1. The higher the injury severity scores the greater the deficiency of fibrinogen (30,31,32). Schlimp et al. studied the possibility of estimating fibrinogen levels based on hemoglobin, base excess and injury severity score. Their data showed that with higher ISS, patients had lower fibrinogen levels (56% in ISS >=16 vs 93% in ISS>=50) (30). Rourke et al. found a similar association when he studied fibrinogen levels in 517 trauma patients (31). In another study conducted by Tauber et al (32), they found that 26% of their cohort study patient (mean ISS 35) had a fibrinogen level less than 2g/L.

2. The higher the value (lower threshold) for abnormal fibrinogen the higher the incidence of fibrinogen deficiency (29,30,31,32,27,23).

3. There is a strong association between fibrinogen levels and mortality (29,31). Hagemn et al. studied the prevalence of hypofibrinogenaemia in 1133 trauma patients (29). Hypofibrinogenaemia was present is 8.2% and 19.2% when setting low fibrinogen values as <=1.5g/L and <2g/L respectively. In addition, they noticed a relationship between fibrinogen levels and mortality in their piecewise linear regression model. A breakpoint for optimal fibrinogen concentration at 2.29g/L was identified. Odds of death were reduced by a factor of 0.08 with every unit increase in fibrinogen below this point. The relationship between fibrinogen level and mortality was also addressed by Rourke et al. (31). In this study non-survivors at 24h compared to survivors had a lower fibrinogen level by 51%. In addition, The odds of death reduced by a factor of 0.22 during the first 28 days for every 1 g/L increase in admission fibrinogen level.

Davenport et al. highlighted another aspect of hypofibrinogenaemia in his study (16). Comparing patients with and without high aPC, they found that fibrinogen only fell below 1.5g/L in patients with high aPC despite having high thrombin levels in both groups. On the other hand, PAP (plasmin-antiplasmin complex) levels were strongly inversely correlated with fibrinogen (R² =0.23, p<0.01). This suggested that fibrinogen loss is a result of plasmin-mediated fibrinogenolysis rather than a consumption process.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study</th>
<th>Study sample</th>
<th>Cohort</th>
<th>Definition</th>
<th>Number/study sample</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hagemo</td>
<td>2014</td>
<td>Prevalence, predictors and outcome of hypofibrinogenaemia in trauma: a multicenter observational study.</td>
<td>1133</td>
<td>ISS (16.1), age (37.2), BE (-2.48)</td>
<td>Fibrinogen &lt;=1.5 g/L</td>
<td>93/1133</td>
<td>8.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fibrinogen &lt;2g/L</td>
<td>211/1133</td>
<td>19.2%</td>
</tr>
<tr>
<td>Schlimp</td>
<td>2013</td>
<td>Estimation of plasma fibrinogen levels based on hemoglobin, base excess and injury severity score upon emergency room admission.</td>
<td>676</td>
<td>ISS (27), age (45), 79.6% male.</td>
<td>Low Fib (L) &lt;200mg/dL</td>
<td>75% (L) 54%(CL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hb&lt;12</td>
<td>75% (L) 54%(CL)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hb&lt;10</td>
<td>89 % (L) 73% (CL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hb&lt;8</td>
<td>93% (L) 89% (CL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Critically low Fib (CL) &lt;150mg/dL</td>
<td>66 % (L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BE &lt;-2 mmol/L</td>
<td>66% (L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BE &lt;-6mmol/L</td>
<td>81%(L), 93% (CL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BE &lt;-10mmol/L</td>
<td>89%(L), 78%(CL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ISS&gt;=16</td>
<td>56% (L)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ISS&gt;=25</td>
<td>68% (L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ISS&gt;= 35</td>
<td>88% (L) 67% (CL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ISS&gt;= 50</td>
<td>93% (L) 74%(CL)</td>
<td></td>
</tr>
<tr>
<td>Rourke</td>
<td>2012</td>
<td>Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcome.</td>
<td>517</td>
<td>ISS (14), age (36), 83% blunt, 78% male.</td>
<td>Fib &lt;1.5 g/L</td>
<td>72/517</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fib &lt;1.0 g/L</td>
<td>26/517</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fib &lt;0.8 g/L</td>
<td>15/517</td>
<td>3%</td>
</tr>
<tr>
<td>Tauber</td>
<td>2011</td>
<td>Prevalence and impact of abnormal ROTEM assays in severe trauma patients: results of ‘diagnosis and treatment of trauma induced coagulopathy (DIA-TRE-TIC) study’</td>
<td>271</td>
<td>ISS (35), GCS (13), Age (42), Male 79.6%.</td>
<td>Fibrinogen &lt;200mg dl</td>
<td>71/271</td>
<td>26%</td>
</tr>
<tr>
<td>Johansson</td>
<td>2011</td>
<td>Disseminated intravascular coagulation or acute coagulopathy of trauma shock early after trauma? An observational study.</td>
<td>80</td>
<td>ISS (35), GCS (13), Age (42), Male 79.6%.</td>
<td>Fibrinogen &lt;1 g/L</td>
<td>1/80</td>
<td>0.8%</td>
</tr>
<tr>
<td>Carroll</td>
<td>2009</td>
<td>Early evaluation of acute traumatic coagulopathy by thrombelastography.</td>
<td>161</td>
<td>ISS (20) age (42), 73% male.</td>
<td>Fibrinogen &lt;100mg/dl</td>
<td>18/161</td>
<td>11%</td>
</tr>
</tbody>
</table>

3.4 Hyperfibrinolysis in ATC:

The search resulted in six studies that addressed the prevalence and impact of hyperfibrinolysis in trauma patients. All studies with the reported incidences of hyperfibrinolysis are displayed in table 3. Primary findings indicate the following:

1. The reported incidence in trauma cohorts ranged between 2%-11% (27,32,34,35,37), except for one study, which had a higher incidence of 18%(36). The higher incidence of hyperfibrinolysis in Kashuk et al. study could be explained by the study cohort, which involved trauma patients who ended up receiving blood products during their resuscitation.

2. Hyperfibrinolysis was reported to be significantly related to mortality in all studies (27,32,34,35,36,37). Patients with hyperfibrinolysis had higher ISS, increased risk of death, higher mortality rate and higher transfusion requirements.

3. About half of trauma patients without hyperfibrinolysis will have some evidence of fibrinolytic activation(34,36). Raza et al. investigated the magnitude of fibrinolytic activation in trauma patients very recently (34). They reported that 180 patients out of 288 had a moderate fibrinolytic activation, defined as PAP >1500. This finding is very important as it suggested that the current definition of hyperfibrinolysis by the viscoelastic assays might miss >90% of patients with fibrinolytic activation. Kashuk et al reported a similar importance as 46% of trauma patients who required blood products transfusion had a transient fibrinolysis (TF<15%) (36).

Looking at the pathophysiology behind it, Davenport et al. attributed the fibrinolysis process to aPC pathway (24). It was clear from their data that as levels of aPC increased, D-dimer and PAP levels increased. In fact, they reported, “this tPA dependent process was completely inhibited at normal aPC levels but was massively activated when aPC was high (tPA >20ng/ml: [aPC ≤3ng/ml] PAP 4400 ±3104μg/L vs [aPC >3ng/ml] PAP 21428 ±4972μg/L, p<0.05)”. In addition, they were able to correlate between aPC levels and PAI-1 levels. They found that when aPC levels were less than or equal to 3ng/ml, PAI-1 level was 58ng/ml compared to 31ng/ml when aPC levels were more than 9 (p<0.001). This supported the theory of PAI-1 consumption with higher aPC levels, resulting in more available tPA and hence more fibrinolysis.
Table 3.3: Hyperfibrinolysis incidence in trauma population

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study</th>
<th>Study sample</th>
<th>Cohort</th>
<th>Definition</th>
<th>Number/study sample</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raza (34)</td>
<td>2012</td>
<td>The incidence and magnitude of fibrinolytic activation in trauma patients.</td>
<td>288</td>
<td>ISS (10), age (37), 81.9% male, 79.5% blunt.</td>
<td>Hyperfibrinolysis ML60&gt;15%</td>
<td>15/288</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FA by PAPs &gt;1500 (normal ML)</td>
<td></td>
<td>180/288</td>
<td>59%</td>
</tr>
<tr>
<td>Ives (35)</td>
<td>2012</td>
<td>Hyperfibrinolysis elicited via thromboelastography predicts Mortality in trauma.</td>
<td>118</td>
<td>47.5% ISS &gt;16, 51.7% penetrating, 23.7% GCS&lt;8</td>
<td>Hyperfibrinolysis=EPL&gt;=15%,</td>
<td>13/118</td>
<td>11%</td>
</tr>
<tr>
<td>Tauber (32)</td>
<td>2011</td>
<td>Prevalence and impact of abnormal ROTEM assays in severe trauma patients: results of ‘diagnosis and treatment of trauma induced coagulopathy (DIA-TRE-TIC) study’.</td>
<td>334</td>
<td>ISS (34), Age(43), GCS (11), 77.8% male.</td>
<td>HF: ML60 &gt;15% Fulminant HF: complete clot dissolution by 60 min</td>
<td>23/334</td>
<td>6.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reduction of clot firmness of 16-35%</td>
<td>14/23</td>
<td></td>
</tr>
<tr>
<td>Kashuk (36)</td>
<td>2010</td>
<td>Primary fibrinolysis is integral in the pathogenesis of the acute coagulopathy in trauma.</td>
<td>61</td>
<td>MT 32/61: 52% - ISS 32 Mod 15/61: 25% ISS 29 Mild 14/61: 23% ISS 34</td>
<td>PF: EPL&gt;15% TF: EPL &lt;15%</td>
<td>11/61</td>
<td>18% (34% of MT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28/61</td>
<td>46%</td>
</tr>
<tr>
<td>Carroll (27)</td>
<td>2009</td>
<td>Early evaluation of acute traumatic coagulopathy by thrombelastography.</td>
<td>161</td>
<td>ISS (20), age (42), 73% male,</td>
<td>Hyperfibrinolysis LY60 &gt;15%</td>
<td>3/161 on site</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3/161 on ED (1 pt on site resolved, new pt developed HF on ED)</td>
<td></td>
</tr>
<tr>
<td>Levrat (37)</td>
<td>2008</td>
<td>Evaluation of rotation thrombelastography for the diagnosis of hyperfibrinolysis in Trauma patients.</td>
<td>87</td>
<td>Control (82): ISS (20), Age (29), 78% male, 83% blunt Hyperfibrinolysis (5): ISS (75), Age (30), 80% male, 100% blunt.</td>
<td>Hyperfibrinolysis: a threshold of 18 mm (MCF-EXTEM), 71% (CLI30) and 7% (increase of MCF-APTEM)</td>
<td>5/87</td>
<td>6%</td>
</tr>
</tbody>
</table>

3.5 Platelet abnormalities in ATC:

The search resulted in 6 studies reporting platelet count incidence and 3 studies addressing platelet dysfunction. Table 4 demonstrates all the studies with their incidences and outcomes. The following points were observed:

1. The majority of trauma patients reported in the literature present to the emergency room with a platelet count more than 100,000/ mcL. The incidence of platelet count below this value was found to be less than 6% (15,23,32,38,40). When Hess et al. studied the prevalence of abnormal coagulation tests in 13,290 trauma patients upon admission to the hospital, he reported that platelet count was the least abnormal result in all trauma patients with ISS more than 4 (15).

2. There is a strong relation between decreasing platelet counts and increasing mortality and transfusion requirements. Brown et al. reported a dose dependent inverse correlation between admission platelet counts and 24h mortality and transfusion of PRBC even for platelet counts in the normal range (39). 88.4% of patient who were severely injured and massively transfused with more than10 PRBC in 24h had a platelet count >100,000 in Brown study. Solomon reported a similar findings when compared survivors to non-survivors in his trauma cohort (40). Though only 2 patients out of 163 had a count less than 100,000; platelet count and ROTEM component of platelet were significantly higher in the survivors group.

In the three studies addressing platelet dysfunction, it was observed that platelet dysfunction occurs early after injury in trauma patients. Kutcher et al. (41) and Solomon et al. (40), both used MEA for the platelet function assessment in trauma patients while Wohlauer et al. (42) used TEG mapping. Adenosine Diphosphate ADP, Thrombin Receptor Activating Peptide TRAP, Arachidonic Acid AA and Collagen are used as agonists to activate platelets and measure its reactivity in the MEA. Kutcher et al. studied 101 trauma patient with a median ISS of 23.3. Almost half of these patients had decreased platelet activity on admission to the trauma center. In addition, he identified BD and GCS are independent predictors of platelet hypofunction. In Solomon study, trauma non-survivors group had decreased platelet activity in addition to a significantly lower SBP, lower GCS and higher ISS. Wohlauer et al. data supported Solomon and Kutcher findings of the relation between platelet function and tissue injury and shock. His data reported a significant relation between ADP mediated platelet function and BD>=8 and ISS. Moreover, Wohlauer compared trauma patients to healthy volunteers and showed a similar evidence of reduced platelet activity.
<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Year</th>
<th>Study</th>
<th>Study sample</th>
<th>Cohort</th>
<th>Definition</th>
<th>Number/study sample</th>
<th>Incidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kutcher (41)</td>
<td>2012</td>
<td>Characterization of platelets dysfunction after trauma.</td>
<td>101</td>
<td>ISS (23.3), 31% penetrating, 61.2% brain injury</td>
<td>Low response to any of (ADP, TRAP, AA, Collagen)</td>
<td>46/101</td>
<td>45.5%</td>
<td>All pt had normal plt counts &gt;140</td>
</tr>
<tr>
<td>Wohlauer (42)</td>
<td>2012</td>
<td>Early platelets dysfunction: an unrecognized role in acute traumatic coagulopathy.</td>
<td>Trauma: 51 Healthy: 39</td>
<td>ISS (19), GCS (11.9), 86% blunt injury, 20% brain injury</td>
<td>- Median ADP inhibition (trauma vs healthy) - Median AA inhibition (trauma vs healthy)</td>
<td>86.1% vs 4.2 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solomon (40)</td>
<td>2011</td>
<td>Platelets function following trauma: a multiple electrode aggregometry study.</td>
<td>163</td>
<td>ISS (18), Age (43), 79.7% male</td>
<td>Plt count &lt;100,000</td>
<td>2/163</td>
<td>1.2%</td>
<td>Survivors had significantly higher ADPtest, TRAPtest, plt count &amp; ROTEM component of plt.</td>
</tr>
<tr>
<td>Brown (39)</td>
<td>2011</td>
<td>A normal platelet count might not be enough: the impact of admission platelets counts on mortality and transfusion in severely injured trauma patients.</td>
<td>389</td>
<td>Massively transfused trauma patients (&gt;10 PRBC in 24h).</td>
<td>Platelets counts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tauber (32)</td>
<td>2011</td>
<td>Prevalence and impact of abnormal ROTEM assays in severe trauma patients: results of ‘diagnosis and treatment of trauma induced coagulopathy (DIA-TRE-TIC) study’.</td>
<td>271</td>
<td>ISS (35), GCS (13), Age (42), Male 79.6%.</td>
<td>Low Platelets counts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johansson (23)</td>
<td>2011</td>
<td>Disseminated intravascular coagulation or acute coagulopathy of trauma shock early after trauma? An observational study.</td>
<td>80</td>
<td>ISS (17), Age (46), GCS (13) 68% male, 91% blunt</td>
<td>Plt count &lt;100,000</td>
<td>1/80</td>
<td>0.8%</td>
<td></td>
</tr>
<tr>
<td>Author (ref)</td>
<td>Year</td>
<td>Study</td>
<td>Study sample</td>
<td>Cohort</td>
<td>Definition</td>
<td>Number/study sample</td>
<td>Incidence</td>
<td>Outcome</td>
</tr>
<tr>
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<td>-----------</td>
<td>---------</td>
</tr>
<tr>
<td>Hess (15)</td>
<td>2009</td>
<td>The prevalence of abnormal results of conventional coagulation tests on admission to trauma center.</td>
<td>13290</td>
<td>ISS≥5, 72.2% male, age (38)</td>
<td>Plt count &lt;100,000</td>
<td>664/13290</td>
<td>5%</td>
<td>In pt with ISS&gt;4, plt count was the least abnormal result.</td>
</tr>
<tr>
<td>Macleod (38)</td>
<td>2003</td>
<td>Early coagulopathy predicts mortality in trauma.</td>
<td>7638</td>
<td>ISS (9), Age (38), 76.2% male</td>
<td>Plt count &lt;100,000</td>
<td>229/7638</td>
<td>3%</td>
<td>Plt count is not a predictive value for mortality</td>
</tr>
</tbody>
</table>

* (n)=median. ISS: injury severity score, plt: platelet, GCS: Glasgow coma scale, ADP: adenosine diphosphate, AA: arachidonic Acid, TRAP: thrombin receptor activating petptide-6
3.6 Endothelial damage & sympathoadrenal activation in ATC:

Glycocalyx degradation is usually measured by syndecan-1 and thrombomodulin levels. When Johansson et al. (43) compared trauma patients with high and low admission syndecan-1 levels, glycocalyx degradation appeared to be associated with higher mortality and higher sympathoadrenal activation. Yet, he found that both groups had comparable injury severity scores. Only trauma patients with high syndecan-1 levels showed an association between increasing ISS and increasing tissue and endothelial damage, inflammatory response, depletion of protein C and hyperfibrinolysis.

The same group investigated the relation between traumatic coagulopathy and the activation of the sympathoadrenal system (45). They found that adrenaline levels are closely related to tissue damage, inflammation, abnormal coagulopathic parameters and hyperfibrinolysis. Adrenalin level was also found to be an independent predictor of mortality. In another study, Ostrowski and Johansson hypothesized that autoheparinization might also play a role in the endogenous process of acute traumatic coagulopathy (44). Considering that the endothelial layer constitute one quarter of intravascular volume, release of heparin-like substance once its injured could be significant enough to contribute to the coagulopathic disturbance. Autoheparinization was evident in 5% of their study population and it was associated with 4-fold increase in syndecan-1 levels. Patients with autoheparinization had more severe injuries and received more transfusions in the first 24 hours.
Chapter 4. Discussion

Preventing deaths from exsanguination after severe injury is an important public health, scientific and clinical challenge. ATC is a major contributor to these potentially preventable deaths and rapid reversal of trauma related hemostatic abnormalities provides the best chance of arresting non-surgical hemorrhage. To accomplish this, a thorough understanding of the pathophysiology of ATC is required in order to inform clinicians on the best modalities for rapidly diagnosing and reversing ATC. This study provides an in depth review and summary of the current knowledge relating to the pathophysiology of ATC which provides clinicians with the directions they need to optimize diagnostic and therapeutic strategies.

In general, this study has demonstrated that the pathophysiology of ATC is far more complicated and heterogeneous than originally recognized, which questions the validity of current diagnostic and therapeutic strategies aimed at correcting ATC. Specific components of ATC that have been identified include the following. There is a strong association between aPC pathway and ATC. In the synergistic presence of shock and tissue injury, protein C gets activated due to the presence of soluble TM that binds to thrombin. Once protein C is activated it consumes Factor V and relieves the inhibition from plasmin, leading to more fibrinolysis. This was evident by the reduction in FV .PAI-1 and increased D-dimer levels. The role of aPC as a central component in ATC was proven in recently published animal models (24, 61). Using selective inhibition of the anticoagulant effect of aPC, mice with induced trauma and hemorrhage were protected from developing coagulopathy Davenport et al. tested the effect of tissue injury and shock on a transgenic thrombomodulin knock-in mice (TMKI) module (24). These mice and compared to normal wild type (WT) mice had preserved clot strength and significantly less prolongation of PT and aPTT for 60 minutes. Chesebro et al. reported similar findings with another mouse model (61). In these models, blocking the anticoagulant effect of aPC protected against developing ATC.

It is important to note that aPC has anti-inflammatory and cyto-protective properties in addition to its anticoagulant feature. The evidence of a potential role for aPC in the treatment of thrombosis, sepsis, fibrotic heart disease and thrombotic stroke is rapidly expanding (72). It exerts its cyto-protective properties through endothelial cell protein C receptor and protease-activated receptor-1 (PAR-1). Chesebro et al. tested the effect of complete inhibition of aPC pathway by blocking both the anticoagulant and the cytoprotective components of aPC in mouse with induced trauma and hemorrhage (61). Mouse in this module had a mortality rate of 100% within 45 minutes of shock with histological evidence of pulmonary thrombosis and perivascular hemorrhage. This shows that aPC related-coagulopathic disturbance is actually balanced by its anti-inflammatory and cyto-protective properties. Together, these properties modulate the outcome in response to tissue injury and shock. Human studies are needed in order to apply this knowledge in the real clinical trauma settings.

Clotting factor abnormalities in ATC are well documented and this review suggests that FV is the main factor getting depleted. The relation between higher levels of aPC and lower FV supported the theory that this change is mediated by aPC. FVIII levels varied from different studies and some studies reported higher than normal level, this
could be attributed to the fact that this factor is also an acute phase reactant. So, two processes of; increase production and increase deactivation occurs at the same time. But, could this be the main reason behind ATC? And could blocking this anti-systemic effect or supplying the body with FV results in reversing the hemostatic changes? Interestingly, though factors get depleted and their activities get reduced in ATC, thrombin generation is preserved and actually found to be higher in patients with ATC. Thrombin is the last product of the coagulation cascade; so how significant is the CF role in ATC? It appears that even though there is an aPC-mediated reduction in CF activity, this effect is not significant enough to be solely responsible for the complex ATC picture.

Applying this into clinical practice and comparing available sources of CF, FFP is the only source that contains both factors (FV and FVIII). Multiple studies have shown the efficacy of transfusing FFP earlier and with higher ratios in improving outcomes in trauma related shock. On the other hand, many investigators argued that many of these studies had a high survivability bias “is giving higher ratios of FFP the cause of the better outcome? Or is it that patients who survived longer received more FFP?” In addition, the association between FFP use and subsequent ARDS and prolonged ICU and ventilation days addresses the need for caution and a search for other products for volume resuscitation and ATC reversal. With all of these issues and with the knowledge that thrombin generation is preserved regardless of CF deactivation questions the need of routinely transfusing FFP in trauma and identifies the need for other options to replace the volume loss.

This review has identified a very important role for fibrinogen and hyperfibrinolysis in ATC. It was more evident in patients with more severe injuries and hypo-perfused. Worse outcomes and increased mortality were significantly associated with lower fibrinogen levels and higher degree of fibrinolysis. Two things are occurring in ATC that affect the amount of fibrin available; increased lysis of fibrinogen and fibrinolysis resulting in decreased clot strength. An expanding base of evidence relates both of these processes to aPC. These findings strongly suggest that a higher target level of fibrinogen along with inhibition of fibrinolysis should be aimed for in trauma resuscitation thereby providing more available fibrin.

In regards to fibrinogen, the variability in defining a threshold for clinically relevant deficit and therefore the need for replacement was obvious and made reporting an overall incidence for this deficit difficult. It was clear that by setting a high threshold (lower fibrinogen value), the chance of missing trauma patients who might need fibrinogen administration is high. Recently, Hagemn et al. proposed a new fibrinogen target of 2.26 in trauma population and reported that lower levels were associated with increased mortality (29). This threshold is lower than all reported previous ones and is specific to trauma population. Clinical trials investigating the efficacy of fibrinogen administration to correct the coagulopathy in trauma setting are still lacking. Few retrospective studies reported better outcome or decreased transfusion requirements in trauma patients treated with fibrinogen (62,63). Most studies recommend administration of fibrinogen concentrates 3-4g or Cryo 50mg/kg to maintain fibrinogen level >1g/L (64) or to raise MCF to 10-12 mm in the FIBTEM assay (fibrin based clot strength) in ROTEM (63).
Interestingly, the use of fibrinogen to correct coagulopathy in massively bleeding patients has been tested in other surgical areas. There are a few studies published investigating its efficacy in reducing postoperative bleeding and transfusion requirements in cardiac surgeries, vascular surgeries and gynecological surgeries (65,66,67,68). Theses studies suggested that fibrinogen concentrates administration, either prophylactically or ROTEM guided, managed to decrease intra and postoperative bleeding and to decrease platelets and FFP transfusion. The ability of fibrinogen to correct the coagulopathic disturbance and decrease transfusion requirements is a very important finding. Perhaps replacing FFP with Cryo or fibrinogen concentrates, which provide higher amounts of fibrinogen in lesser volumes, should be considered in trauma resuscitation.

In regards to hyperfibrinolysis, it seems that the current agreed on definition of hyperfibrinolysis in ATC might need to be revised. Raza et al. and Kashuk et al. both detected the presence of fibrinolytic activation in their trauma cohorts which was missed when hyperfibrinolysis defined as LY>15% (34,36). Increased fibrinolytic activation was linked to mortality in both groups. Raza et al demonstrated a 12 fold increase in mortality when compared trauma patients with moderate fibrinolytic activation (defined as PAP >1500) to no fibrinolytic activation. Unfortunately, PAP levels are typically measured by ELISA methods that are not amenable to the acute setting of trauma resuscitation.

In the clinical setting, even though the exact mechanism by which tranexamic acid works in ATC is not fully understood (antifibrinolytic and/or anti-inflammatory), evidence supporting its use earlier in trauma is substantial. After the CRASH II clinical trial, the use of tranexamic acid in trauma resuscitation was highly recommended and adopted by most centers. MATTERs study followed in 2011 and applied the use of tranexamic acid in the military setting in Afghanistan (69). This study showed that tranexamic acid use resulted in 6.5% absolute reduction in mortality. An important observation was noted in MATTERs, which lead to MATEERs II study in 2012. They observed that the tranexamic acid group patients received higher amounts of fibrinogen-containing Cryo. So, in MATEERs II they compared the survival of combat patients who received Cryo with tranexamic acid, tranexamic acid alone, Cryo alone and no Cryo- no tranexamic acid (70). Mortality rates were 11.6%, 18.2%, 21.4% and 23.6% in each group respectively. Groups receiving tranexamic acid with and without Cryo resulted in lower mortality even though they had greater ISS and received more PRBC. This builds more value to the importance of fibrinolysis inhibition and fibrinogen administration in ATC.

It was noted that platelet activity plays a potentially more important role in ATC compared to platelet counts in the review results. Platelet count might not be very useful to guide platelet concentrate transfusion at this early stage of trauma since most of trauma patients will present with normal values. On the other hand, results showed that reduction in platelet activity is evident very early in trauma and strongly associated with ATC main drivers; injury severity and shock. Many ideas were suggested explaining the reduction in platelet activity, including the effect of acidosis, hypothermia and “exhausted platelet syndrome”. Exhausted platelet syndrome is a phenomena that describe exhausted circulating platelets following an over activation state. In trauma, due to shock and severe tissue injury, ADP gets released into the circulation in excessive amounts resulting in platelet hyper-activation that eventually
consumes it and ends up with poorly responsive platelets. Decreased responsiveness of platelets to ADP and its association with poor outcomes was reported in different studies in trauma (40,41,42).

The challenges of measuring platelet activity in trauma setting have been raised and prophylactic platelet transfusion has been recommended. Platelet mapping assay in TEG appears promising. But, this assay takes at least 30 minutes to fully obtain the results making it real-time efficacy doubtful. Prophylactic transfusion of platelets with PRBC and FFP showed improved outcomes and survival (71). Current guidelines recommend transfusing platelets prophylactically in 1:1:1 ratio with PRBC and FFP in massively bleeding patients. Interestingly, these are the same patients who will present with normal platelet counts. So, prophylactic platelet transfusion is necessary to replace the deactivated platelets rather than insufficient amount of platelets till a real-time patient-tailored technology is developed.

In trauma patients, tissue injury and shock status mediate a generalized inflammation and sympathoadrenal activation. These changes cause a systemic endothelial permeability leading due the release of small molecules like syncaden-1 and heparin like molecules into the blood circulation, which affect the overall hemostatic status. Higher glycocalyx degradation, adrenalin levels, inflammatory markers and autoheparinization were associated with higher mortality and were evident early. Surprisingly, in Johansson et al. study patients with high and low syncaden-1 levels had similar injury severity scores (43). This suggests that, perhaps the endothelial damage is mediated largely by the response taken towards trauma and the resuscitation strategies rather than the amount of tissue damage caused by the injury itself. So does endothelial damage and sympathoadrenal activation contributes more to TIC rather than ATC? It's important to note that this complex inflammatory status is only one component of ATC and extensive research is currently being conducted in this specific field. Which one starts first, and how different components contribute to the overall ATC might be clear after more years of research.

This review is the first of kind to our knowledge that addresses abnormalities in ATC in all its different hemostatic components and formulated into illustrative tables with incidences and outcomes. Only by collating and summarizing the published literature in this manner can clinicians obtain vital new knowledge from a synthesis of different studies enabling better conclusions and clinical decisions. While the utility of this review is considered self evident, the following limitations were noted. First, there are only few RCT conducted in the trauma field, so most of the results obtained in our study are from observational studies which carry less strength. Second, in the studies included, large degree of heterogeneity was found in the trauma cohort, diagnostic tool and intervention strategies, which made our comparison and incidence reporting challenging. Third, ATC pathophysiology is often investigated in animal models and these were not included in this review. Fourth, knowledge of ATC is rapidly expanding with a large pool of articles published related to the topic. Studies focusing more on the clinical implication of ATC were chosen in this review and others were excluded in preference to the main authors.
Conclusion:

ATC is an endogenous state of hypo-coaguloability in severely injured trauma patients, which contributes to lethal hemorrhage. This state is complex, multifactorial and dynamic and starts at the time of injury before arrival to the hospital. Shock and severe tissue injury are the main drivers of ATC. Iatrogenic coagulopathy by the subsequent acidosis, hypothermia and hemodilution adds to ATC resulting in the overall TIC. aPC plays a major role behind ATC pathophysiology and mediates trauma patients’ outcomes through its various pathways. While depleted coagulation factors (particularly FV) have been recognized as a component of ATC it is increasingly apparent that early fibrinogen depletion and fibrinolysis play major roles in ATC pathophysiology. New empiric resuscitation protocols addressing early fibrinogen replacement and antifibrinolytic drugs administration should help address these two hemostatic derangements which are not adequately covered by the current practice of 1:1:1 with FFP as the primary source of replenishment. The goal of real-time patient-tailored directed therapy is dependent on a thorough understanding of the pathophysiology of ATC, rapid and appropriate diagnostic tools to identify the deficits present, and appropriate therapeutic blood products to reverse the identified deficits. Research about the endothelial damage and sympathoadrenal role in ATC, effect of aPC anticoagulant property block in human ATC studies and RCTs comparing current 1:1:1 practice with upfront fibrinogen and TXA administration and/or with TEG/ROTEM guided resuscitation are needed. New knowledge of ATC is rapidly expanding requiring regular review and dissemination to inform clinicians and guide appropriate ATC treatment.
15- Hess JR, Lindell AL, Stansbury LG, Dutton RP, Scalea TM. The prevalence of abnormal results of conventional coagulation tests on admission to a trauma


24- Davenport R, Guerreiro M, Frith D, Rourke C, Platton S, Cohen M, Brohi K. Activated Protein C Dependent Fibrinolysis and Fibrinogenolysis are central to Acute Traumatic Coagulopathy. ******


33- Basic clinician training. Module 5 “ Fibrinolysis and hyperfibrinolysis TEG Analysis. TEG5_analysis ppt.


73- Figure 1.5.1 Trauma Induced Coagulopathy. Created by the thesis author AlMaawali AK. 2014 March 28.


