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TACTIC: Trans-Agency Consortium for Trauma-Induced Coagulopathy

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SUMMARY

Trauma-induced coagulopathy (TIC) includes heterogeneous coagulopathic syndromes with different underlying causes, and treatment is challenged by limited diagnostic tests to discriminate between these entities in the acute setting. We provide an overview of progress in understanding the mechanisms of TIC and the context for several of the hypotheses that will be tested in “TACTIC”. Although connected to ongoing clinical trials in trauma, TACTIC itself has no intent to conduct clinical trials. We do anticipate that “early translation” of promising results will occur. Functions anticipated at this early translational level include: 1. Basic science groundwork for future therapeutic candidates; 2. Development of acute coagulopathy scoring systems; 3. Coagulation factor composition-based computational analysis; 4. Characterization of novel analytes including tissue factor, polyP, histones, meizo and α -thrombin-antithrombin complexes, factor XIa, platelet markers of activation and trauma, signatures of protein C activation and fibrinolysis markers; 5. Assessment of visco-elastic tests and new point-of-care methods.

INTRODUCTION

Trauma is the major cause of death and disability in young adults [1–3]. Worldwide, one in seven deaths is due to injury, and trauma cases are expected to rise to 1 in 5 in the next 15 years, despite continuing advances in resuscitation, trauma surgery, and critical care [1, 3, 4]. Perturbations in blood coagulation present vexing challenges for trauma surgeons, who may need to abandon operations [5], and hemorrhage is responsible for most otherwise survivable deaths in military and civilian trauma [6–9]. Despite massive transfusions of 10 or more units of blood, coagulopathy is often irreversible and lethal [8, 10, 11]. Clinical management is challenged by heterogeneous coagulopathic syndromes leading either to hemorrhage or thrombosis, and an absence of diagnostic tests to discriminate between these entities [6–8, 12, 13]. Efforts to control hemorrhage and restore circulatory homeostasis, coordinated between trauma surgery, emergency medicine, anesthesiology, and transfusion medicine, are central to the modern approach to trauma [14, 15].

Two major obstacles have limited mechanistic and translational research progress in TIC: 1) Difficulty in obtaining longitudinal and well-phenotyped clinical samples from trauma

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patients, particularly in the minutes immediately following injury, and 2) Challenge in establishing a cooperative effort among clinicians and basic scientists to address TIC research questions. The Department of Defense (DoD) recently initiated a large-scale clinical trials program in the civilian trauma environment addressing treatment in pre-hospital and early hospital settings (Appendix). These trials will answer specific therapeutic questions about early administration of plasma and the use of tranexamic acid to block fibrinolysis, with practical implications on patient care. The DoD's Systems Biology Coagulopathy of Trauma Consortium, conducting a multi-center genomic and proteomic assessment of longitudinal samples from civilian trauma subjects, developed standard operating procedures for blood sampling and clinical data abstraction in the three years preceding the start of the trials, and also continues to enroll patients. Together, these trauma studies are expected to accrue over 2000 patients. Capitalizing on this opportunity, the National Institutes of Health (NIH) and DoD implemented a trans-agency partnership to link clinical investigators in the ongoing DoD studies with basic scientists. The TACTIC Research Program (<http://www.tacticproject.org>) includes 12 Basic Science Projects conducted by 21 Investigators across 11 different institutions (Appendix). A comprehensive review of all the hypotheses and specific aims is outside of the scope of this paper; rather, we provide an overview of recent progress in understanding the mechanisms of TIC and the context for several of the hypotheses to be tested in TACTIC.

BACKGROUND

As early as 1954, trauma surgeons in Korea recognized casualties with uncontrolled hemorrhage, associated with abnormal prothrombin (PT) and partial thromboplastin times (PTT) [16]. It was known at the time that hemorrhage induces a biphasic response, with initial acceleration in clotting, followed by shock and hypocoagulability, which was not correctable with blood cell transfusions. Because coagulopathy correlated with number of transfused blood units, the mechanism was attributed to coagulation factor and platelet consumption, compounded by dilution due to intravenous fluids. Fifteen years later in Viet Nam, coagulopathy was reported in association with thrombocytopenia and fibrinolysis, suggesting that “non-lethal episodes of disseminated intravascular coagulation” accompanied recovery from severe trauma and shock [17]. Over the next decade, accumulating evidence suggested that this model was incomplete. For example, both hypothermia and acidosis were shown to contribute to coagulopathy [18]. In the 1980s, the “viscous bloody cycle” of bleeding after trauma was proposed [19]. Traditional resuscitative protocols involving large volumes of relatively cold fluid (dilution), exposure (hypothermia), and prolonged surgery (more exposure, hypothermia, and bleeding), precipitate metabolic failure (acidosis) in a positive-feedback cycle leading to coagulopathy and hemorrhage [10, 20]. The resulting cycle of acidosis, hemodilution, and hypothermia, also called the “lethal triad”, has more recently been incorporated into the term “iatrogenic traumatic coagulopathy” (ITC) [8]. The abnormalities associated with ITC have been partially characterized *in vitro*, in animal models, and in extensive clinical human research [21–25]. This also provided the basis for the change in surgical practice to “damage control surgery”, in which surgeons limit initial operating time to the bare minimum needed for

control of major hemorrhage and bowel contamination, prioritizing the prevention of coagulopathy [19].

More recent clinical data has led to a departure from the notions that coagulopathy after trauma is fundamentally similar to DIC or that it is iatrogenic. It is now clear that many trauma patients have an established coagulopathy at initial medical contact, before resuscitation, reflected by terminology including acute coagulopathy of trauma-shock (ACoTS), acute traumatic coagulopathy (ATC), and trauma-induced coagulopathy (TIC) [11, 19, 24, 26, 27]. Several studies have identified distinct categories of TIC(s), mechanistically distinct from ITC or DIC, present on arrival in the ED in approximately 25% of patients with major trauma [7, 22, 28–30]. For example, an elevated PT, in the absence of thrombin or fibrinogen depletion, has been reported in some coagulopathic trauma patients upon emergency department (ED) arrival, arguing against a consumptive coagulopathy [9]. These subjects had higher transfusion requirements, a greater incidence of MODS, longer ICU and hospital stays, and 4x greater risk of mortality. This suggests a subtype of TIC modulated by the protein C pathway, in which hypoperfusion (without consumption of coagulation factors) triggers aPC and systemic anticoagulation.

Activation of the protein-C pathway is a clinically important hallmark of TIC that is modeled in animals by traumatic injury in combination with hypoperfusion (shock) [21]. The biphasic response of this model shows early activation leading to depletion of aPC followed by impaired activation due to downregulation of thrombomodulin and impairment of EPCR. While aPC has been implicated as a primary driver of TIC, and it has a potent anti-coagulant effect, the primary function of aPC in trauma may be cytoprotective [22, 31, 32]. Furthermore, the multiple organ failure caused by trauma and shock are associated are partially mediated by loss of endothelial barrier function [22, 33, 34]. aPC can maintain endothelial barrier permeability, which may protect against pulmonary edema, acute lung injury (ALI), and infection after trauma [35].

Thus, while TIC is characterized by ‘coagulation’ defects, it is increasingly clear that the drivers of traumatic coagulopathy and its sequelae represent complex perturbations in inflammatory and vascular/endothelial biology as well as coagulation/fibrinolysis defects, which may also contribute in TIC syndromes. Indeed it is somewhat naïve to suggest that coagulation and inflammation are separable. Rather they represent a complex *interactome*, which is perturbed by injury and shock. There are temporal links between inflammatory syndrome and coagulation abnormalities after trauma [33, 36–38]. It is also clear that inflammatory and coagulation mediators have significant interplay and multiple overlapping actions (pro/anticoagulant-fibrinolytic and pro/antiinflammatory) [31, 34, 39].

TACTIC HYPOTHESES

The first TACTIC hypothesis is that blood and tissue cell membranes altered by trauma, or transfused during resuscitation, influence meizothrombin generation and contribute to TIC. Meizothrombin (mIIa), with thrombomodulin, is an important effector of activated protein-C (aPC) formation and down-regulation of the coagulant response. Prothrombin can proceed through two cleavage pathways, both of which ultimately result in thrombin activation [40].

On platelets, the conventional pathway prevails and the only active product is activated thrombin (α IIa) [41, 42]. It was recently determined that not only platelets, but also circulating RBCs, can produce thrombin via the alternate mII pathway [43]. On red cells [43] and other phosphatidylserine (PS)-expressing membranes [40], the reaction proceeds through the catalytically active intermediate mIIa. In static systems, mIIa is rapidly converted to α IIa [40]. However, under flow conditions, mIIa is relatively stable [42]. mIIa's anticoagulant effect is inhibited efficiently by heparin-antithrombin (AT), and it potently activates protein-C [44, 45], inhibits thrombosis after injury [46] and is a potent vasoactivator[47]. Systemic thrombin generation has been implicated in TIC [9, 22], but the relative contribution of meizothrombin (mII) in trauma has not been studied. Surface expression of PS on normal blood cells is tightly controlled, thereby regulating mIIa formation in hemostasis. Cellular damage by mechanical or chemical means may lead to increased PS expression and therefore increased formation of mIIa [48]. Thus, activated cells and cell particles are potential upregulators of the mIIa/Tm expression leading to localized and/or systemic anticoagulation. mIIa production on both native RBC membranes [43] and on the membranes of cell transfusion products, with increased PS during harvesting and storage, may also lead to increased PC activation and causing systemic anticoagulation [49, 50].

Another TACTIC hypothesis is that the coagulation factor XIa is a marker of trauma severity and a causative factor of TIC. Trauma patients have an elevated procoagulant activity in their blood [51, 52], assigned to some extent to an elevated expression of tissue factor (TF) on blood and endothelial cells [28, 53, 54]. However, in many instances there is a discrepancy between the levels of TF measured in those patients and the clinical manifestation of trauma. It was recently shown that trauma patients have circulating active FXIa in their blood [55]. Similar observations were made for patients with cardiovascular and inflammatory diseases [56–62]. Furthermore, the frequency of TF and FXIa occurrence correlated with the severity of trauma and the cardiovascular event. Back-activation of FXI by thrombin is greatly stimulated by platelet polyphosphate (polyP), and almost all of the ability of platelet releasates to promote FXI activation by thrombin is due to the polyP content of the releasates [63]. Platelet polyP may therefore play a critical role in the contributions of FXI to TIC, by providing a positive feedback loop in which polyP promotes FXI activation by thrombin, and FXIa promotes prothrombin activation via activating factor V.

TACTIC will also address mechanisms of platelet dysfunction in the setting of trauma. Trauma affects platelet function through a combination of a) tissue factor and collagen exposure, b) thrombin and plasmin generation, c) endothelial cell dysfunction, and d) the release of DNA, histones, ADP and polyP from damaged cells and/or activated platelets. It is predicted that depending upon the balance of all of these factors, trauma will produce either a hemorrhagic state, a prothrombotic state or a combination of both. Furthermore, it is hypothesized that platelet dysfunction in the setting of TIC arises in part from the desensitization of agonist receptors on the platelet surface, in part from a failure of critical pathways within the platelet signaling network, and in part, from systemic effects arising from endothelial cell dysfunction and the activation of inflammatory cells. Penetrating injuries in the microvasculature evoke a hemostatic response in which a core of fully-

activated platelets is overlaid with an unstable shell of less-activated platelets [64]. Thrombin formation [65] is confined to the inner core of the hemostatic mass, and fibrin deposition co-localizes with thrombin activity. Fibrin deposition also extends into extravascular tissue planes, forming an extended meshwork from extravasated fibrinogen. Platelet signaling mechanisms potentially important in TIC can be evaluated with genetically-modified mice carrying gain- and loss-of-function mutations in collagen, thrombin, TxA2 and ADP-dependent signal pathways [64, 66]. Mice in which microsomal Prostaglandin E synthase-1 (mPGES-1) was deleted selectively in endothelial and vascular smooth muscle cells (vascular mPGES-1 knockouts) have determined inflammatory elements that modulate platelet function [67]. mPGES-1 is downstream of the immediate early gene cyclooxygenase-2, is rapidly upregulated in response to inflammatory stimuli, and its product Prostaglandin E2 increases vascular permeability, enhances leucocyte transmigration and modulates platelet function [68]. Vascular mPGES-1 deletion does not affect thrombus formation in mice without inflammation [68]. In addition, recent clinical data from specialized visco-elastic “platelet-mapping” assays in trauma indicates that ADP-induced platelet activation could be more impaired than other activating pathways (such as arachidonic acid or kaolin/ thrombin) [69–71], suggesting that changes in ADP receptor regulation or function may play a role.

Another area of interest in TACTIC is the interface between coagulation and fibrinolysis. It is increasingly clear that some subtypes of TIC involve platelet-independent mechanisms of fibrin clot instability with decreased FXIII, TAFI, and PAI-1; this category of TIC appears to be an important cause of early death due to hemorrhage [72–75]. It is hypothesized that fibrin degradation products from systemic sites differ from those produced at major injury sites. Fibrin structure is related to the intensity of thrombin generation during its formation [76–86]. Increased tissue-type plasminogen activator (t-PA) secretion [87, 88] and potentially urokinase-type plasminogen activator from the cerebral vasculature [89] coupled to antiprotease depletion can also potentiate a hemostatic imbalance. The primary enzyme responsible is plasmin, but other proteases could also contribute to fibrinolysis. MS proteomic analysis shows that trauma/hemorrhagic shock depletes antiproteases and introduces unexpected proteases such as elastase [90–93]. In some cases, fibrinolysis can be completely shut down [94], and the degree of an individual’s overall fibrinolytic potential is likely to be a key modulator of TIC.

Inflammatory mechanisms appear to enhance TF expression in trauma-induced coagulopathy. TACTIC will also test the hypothesis that TF and complement work synergistically to initiate and amplify coagulation after trauma and hypoperfusion. Complement is activated early after trauma in humans [95, 96]. The mannose-binding lectin (MBL)-initiated, alternative pathway amplified activation of complement occurs immediately after trauma and hypoperfusion and is strongly associated with TIC [38, 97]. Complement and coagulation are also linked in multiple organ failure [98] and in various thrombotic vascular disorders due to shedding of endothelial heparin and platelet activation. “Danger signals” released from injured tissue following traumatic injury and ischemia can induce [99–101] and activate TF on macrophages through P2X7 signaling [102]. Complement C5a-dependent redox changes in conjunction with C7-dependent

phosphatidylserine exposure can also rapidly activate preexisting pools of TF on leukocytes [103, 104].

These danger signals can have multiple effects beyond macrophage activation. An additional TACTIC hypothesis is that cellular danger signaling and/or complement activation in the context of tissue injury provides a coagulation trigger that is unmasked by ischemia and possibly propagated by reperfusion. Specifically, activation of tissue factor (TF) and complement cause initially amplified and subsequently impaired generation of aPC and deregulated hemostasis in TIC. Hypoxia and/or complement activation causes priming of endothelial cells resulting in increased expression of cytokines, thrombomodulin and EPCR to initiate TIC. This primes neutrophils for excessive ROS production and protease release, leading to additional endothelial damage, which further impairs coagulation. Products released from damaged cells, have been called danger-associated molecular pattern molecules (DAMPs), including high mobility group box-1 (HMGB-1), histones, mitochondrial and nuclear DNA, non-coding RNA, purine metabolites, and many other molecules [105, 106]. DAMPs can have a local, paracrine effect, or they can be released into the systemic circulation; in either case, they are recognized by pattern recognition receptors, including members of the toll like receptor (TLR) family. These receptors are also utilized to recognize non-self-antigen produced from pathogens, such as lipopolysaccharide, bacterial DNA, and viral RNA. DAMPs and TLRs are important to exacerbating tissue injury in the setting of trauma and the development of coagulopathy [33, 37, 38]. In the setting of cytokine release, coagulopathy, and activated endothelium, recruitment and priming of neutrophils amplifies their release of ROS and tissue-damaging proteases, resulting in organ injury [107–112]. In other models of inflammation, neutrophils have been shown to produce extracellular traps (NETs), novel DNA structures covered with granular proteins that are released in the vasculature and have the capacity to injure surrounding host cells [113, 114].

Among the danger signals, histones in particular are increased in trauma patients and associated with poor prognosis [34]. The histone-mediated enhancement of coagulation seen in other diseases may be even more pronounced in trauma patients, especially those with the highest histone levels. Infusion of histones leads to a DIC like state with platelet activation and fibrin deposition in the tissues. Blocking the histones, especially histone H4, dampens the DIC like response, decreases inflammation and protects mice against LPS and reperfusion injury [32, 115]. Finally, histones activate platelets and generate potent thrombin generation in platelet rich plasma [116], possibly through then elaboration of polyP and/or via histone:polyP interaction.

Because ECs vastly outnumber circulating immune cells, lining even the smallest capillary beds, the endothelium is uniquely positioned to serve as the primary immune sensor for danger signals. TACTIC will test the hypothesis that histones activate the endothelium in low concentrations, in combination with polyP and proinflammatory cytokines, through interactions with TLR and other cell surface receptors causing transient receptor potential (TRP) and other Ca^{2+} channels to produce endothelial signals. Toxic concentrations of these metabolites can develop under low-flow conditions of shock, leading to Ca^{2+} overload and endothelial dysfunction. This attenuates barrier function, causing edema and MODS, and impairs thrombomodulin/protein C activation, contributing to TIC. There is evidence that

endothelial cells are activated and injured by traumatic shock [117, 118]. Elementary Ca^{2+} signals through transient receptor potential V4 (TRPV4) channels in the endothelium modulate blood flow at exceedingly low levels of activation [119]. At higher levels, TRPV4 channel activation leads to Ca^{2+} overload [119], loss of EC barrier function, pulmonary edema, and circulatory collapse [120]. Histones potently activate TRPV4 channels suggesting a role in endothelial signaling after trauma (K Freeman, unpublished). ECs are coupled electrically to each other, and histone stimulation causes both local and propagating Ca^{2+} signals. Trauma can also induce nitric oxide synthase expression in the endothelium [121]. Endothelial Ca^{2+} and nitric oxide signals triggered by the circulating milieu in trauma could provide a basis for this endothelial activation and initiation of TIC. Thus, a proposed mechanism of TIC is disruption of “immunovascular coupling”, the local signaling between the endothelium, blood cells, and circulating factors, which normally directs immune responses to the area of injury to promote coagulation and repair. In TIC, immunovascular signaling is uncoupled by circulating factors such as histones and polyp that reach abnormally high concentrations in the systemic circulation under low-flow conditions of shock. This causes overwhelming endothelial activation, in a positive feedback loop between ECs, neutrophils, platelets, and circulating factors, ultimately leading to inflammatory tissue damage, barrier dysfunction and worsening coagulopathy.

STUDY DESIGN

The TACTIC Research Program organization structure includes a Coordinating Center (CC) that links the 4 DoD Clinical Trials, the Early Translational Applications Group (ETAG), and Basic Science Projects, to a shared Repository. The Basic Science Projects include 12 hypothesis-driven research studies conducted by 21 investigators at 11 centers. Coordinated sample collection is an essential component of TACTIC and creates a unique mechanism for basic science investigators to gain access to a large number of temporal and longitudinal trauma patient samples with linked clinical data and use those samples to conduct fundamental research into the pathophysiology of TIC. Importantly, harmonization of blood sampling and clinical data abstraction methods across trauma centers occurred in advance of patient enrollment in the clinical trials, with a Manual of Operations initially developed by the Systems Biology Coagulopathy of Trauma Consortium. Previous experience with the thrombolysis in myocardial infarction (TIMI) trial [122] showed that samples obtained with ordinary anticoagulants (citrate, EDTA), which do not block the fibrinolytic system, were compromised by post-phlebotomy modification of the protein composition. In the trauma environment, the potential for ex-vivo artifact is a particular concern, because pro/anticoagulant, pro/antifibrinolytic, inflammatory cell and tissue proteases are upregulated. Therefore, blood samples for proteomic analysis in the TACTIC studies are drawn into specialized evacuated tubes containing inhibitors to serine, metallo-, aspartyl-, cysteine and collagen proteases, to prevent post-phlebotomy protein alterations that would otherwise occur.

To provide a comprehensive clinical assessment of coagulopathic bleeding in trauma, standard laboratory tests of coagulation including the plasma-based prothrombin time (extrinsic pathway) and partial thromboplastin time (intrinsic pathway), platelet count, and fibrinogen level are measured. In addition, visco-elastic assessment of whole blood

coagulation with thromboelastography (TEG, Haemonetics, Niles, IL) or thromboelastometry (ROTEM, Tem International, Munich, Germany) are used to provide a more comprehensive assessment of clot formation and fibrinolysis using standard protocols [13, 123]. Other novel point-of-care diagnostics are also being tested as part of TACTIC.

New technology and analytical tools will be provided to ETAG to test the potential for clinical feasibility on a small scale. Technology that proves successful in ETAG will be utilized to analyze repository samples and will ultimately be exported to the DoD clinical centers to develop mature, extended hypothesis testing. Thus, data obtained from the ongoing DOD trials are fed back into a funnel of basic science investigation, to produce a data-driven comprehension of TIC. We believe this broad-based approach will lead to significant in-roads into the complex clinical syndrome of TIC, providing novel mechanistic understanding and diagnostics, ultimately advancing the field to benefit patients with acute traumatic injuries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

TACTIC Investigator list

Kenneth G. Mann (PI – Coagulation Component), Charles T. Esmon (PI – Inflammation Component), Stephen Wisnewski (PI – Coordinating Center), Russell P. Tracy (PI – Respository), Andrei L Kindzelski (NIH Program Officer), Anthony Pusateri (DoD Program Officer), Anirban Banerjee, Lawrence Brass, Kathleen Brummel-Ziedins, Saulius Butenas, Mitchell Cohen, Scott Diamond, Kalev Freeman, Ernest E. Moore, Mark T. Nelson, Myung Park, Wolfram Ruf, Jeffrey Shupp, Jason Sperry, Bruce Spiess, and Brian Zuckerbraun

Clinical Studies Linked to TACTIC

- Control of Major Bleeding After Trauma (COMBAT): A Prospective, Randomized Investigation of Pre-Hospital Plasma for The Resuscitation of Traumatic Hemorrhage and Treatment of Acute Post-Injury Coagulopathy, Principal Investigator: Moore
- Prehospital Use of Plasma for Traumatic Hemorrhage (PUPTH), Principal Investigator: Spiess
- Prehospital Air Medical Plasma Trial (PAMP), Principal Investigator: Sperry
- Study of Tranexamic Acid During Air Medical Prehospital Transport (STAAMP), Principal Investigator: Sperry
- Systems Biology for Biological Responses to Severe Hemorrhage, Investigators: Cohen, Freeman, Pusateri, Shupp

Abstracts submitted to the 2015 ISTH that have utilized support from TACTIC

- Bouchard BA, Keith HN, Lavoie EM, Orfeo T, Mann KG: Microparticles generated during storage of packed red blood cell units support thrombin generation
- Butenas S, Gissel M, Park MS: Factor XIa and tissue factor activity in trauma patients
- Butenas S, Manning C, Freeman K: Factor XIa, factor IXa, and tissue factor activity in trauma patients
- Esmon CT: Protein C (APC) pathway functions in inflammatory diseases

- Gajsiewicz JM, Travers RJ, Smith SA, Morrissey JH: Nucleic acids and polyphosphate as modulators of coagulation
- Hebbard CF, Smith SA, Breitenfeld RM, Klein MA, Morrissey JH: Polyphosphate decay in serum is chemical, not enzymatic
- Orfeo T, Keith HN, Lavoie EM, Bouchard BA, Gissel M, Fung M, Mann KG: Prothrombin activation in packed red blood cell units over their storage lifetime
- Travers RJ, Baker CJ, Breitenfeld RM, Drake M, Zhang X, Esmon N, Esmon CT, Morrissey JH: Anti-polyphosphate antibodies as anti-inflammatory/anticoagulant therapeutics
- Zhu S, Travers R, Morrissey J, Diamond S: Role of FXIIa, FXIa, and platelet-derived polyphosphate in thrombin generation using human whole blood perfused over a collagen/tissue factor surface