Mechanisms of early trauma-induced coagulopathy: The clot thickens or not?

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ABSTRACT: Traumatic-induced coagulopathy (TIC) is a hemostatic disorder that is associated with significant bleeding, transfusion requirements, morbidity and mortality. A disorder similar or analogous to TIC was reported around 70 years ago in patients with shock, hemorrhage, burns, cardiac arrest or undergoing major surgery, and the condition was referred to as a "severe bleeding tendency," "defibrination syndrome," "consumptive disorder," and later by surgeons treating US Vietnam combat casualties as a "diffuse oozing coagulopathy." In 1982, Moore's group termed it the "bloody vicious cycle," others "the lethal triad," and in 2003 Brohi and colleagues introduced "acute traumatic coagulopathy" (ATC). Since that time, early TIC has been cloaked in many names and acronyms, including a "fibrinolytic form of disseminated intravascular coagulopathy (DIC)." A global consensus on naming is urgently required to avoid confusion. In our view, TIC is a dynamic entity that evolves over time and no single hypothesis adequately explains the different manifestations of the coagulopathy. However, early TIC is not DIC because an increased thrombin-generating potential in vitro does not imply a clinically relevant thrombotic state in vivo as early TIC is characterized by excessive bleeding, not thrombosis. DIC with its diffuse anatomopathologic fibrin deposition appears to be a latter phase progression of TIC associated with unchecked inflammation and multiple organ dysfunction. (*J Trauma Acute Care Surg*. 2015;79: 301–309.

"For several years, the number of working theories of the hemostatic mechanism greatly exceeded and not always respected the confirmed experimental facts."

—Mario Stefanini, MD (1954)[1]

The statement of Mario Stefanini was made 60 years ago in his address to the NY Academy of Medicine and could easily be applied to today's understanding of hemostasis in all its forms. With new theories, drugs, and devices, the field of hemostasis has expanded exponentially during the last decade and yet continues to expose multiple layers of complexity that drives a special kind of attraction, controversy, and bewilderment among scientists and clinicians alike.

Concept of Homeostasis and Coagulation

Today's understanding of coagulation and its acute changes has its roots firmly embedded in the concept of homeostasis.[2–5] *Homeostasis* is a term coined by Walter Cannon in 1929,[6] which was built on Pfluger's concept of "steady state" (1877), Claude Bernard's concept of "*milieu intérieur*" (1878), and Richet's "stability of the organism" (1900).[6,7] Cannon proposed that life was a *dynamic state of constancy*, with its constituent parts and processes maintained in constant balance or steady state. In the normal state, clot formation and breakdown is recognized as a fine balance between anticoagulant, prothrombotic, and fibrinolytic pathways; a healthy endothelium; circulating platelets; and a highly regulated inflammatory system. When hemostatic imbalances occur, the pendulum can swing in different directions, depending on the type, location, duration, and severity of the injury, with or without blood loss, shock, or infection (Fig. 1). Highly reductionist evidence-based investigations and interpretations in acute- or late-phase coagulopathy are useful only to the extent that they have whole body relevance in health and disease.[13] This is very important when understanding different expressions of the same or distinct clinical entities of coagulopathy.

Trauma-Induced Coagulopathy

Two forms of blood loss can occur from a trauma or injury: (1) direct or anatomic bleeding from the site of injury and/or (2) early coagulopathic bleeding.[14,15] Early coagulopathic bleeding is a systemic oozing phenotype that is routinely diagnosed in trauma patients from prolonged plasma prothrombin time (PT) and activated partial thromboplastin time (aPTT) tests and/or reductions in clot strength and amplitude from rotational thromboelastometry (ROTEM) and thromboelastography (TEG).[4,16–18] The PT and aPTT tests are single-point indicators of clot potential, with clot formation occurring when only approximately 5% of all physiologically relevant thrombin is formed.[19,20] These tests normally take approximately 60 minutes and provide no information on whole blood clot kinetics, elongation and retraction, or platelet-fibrin contributions.[21] Whole

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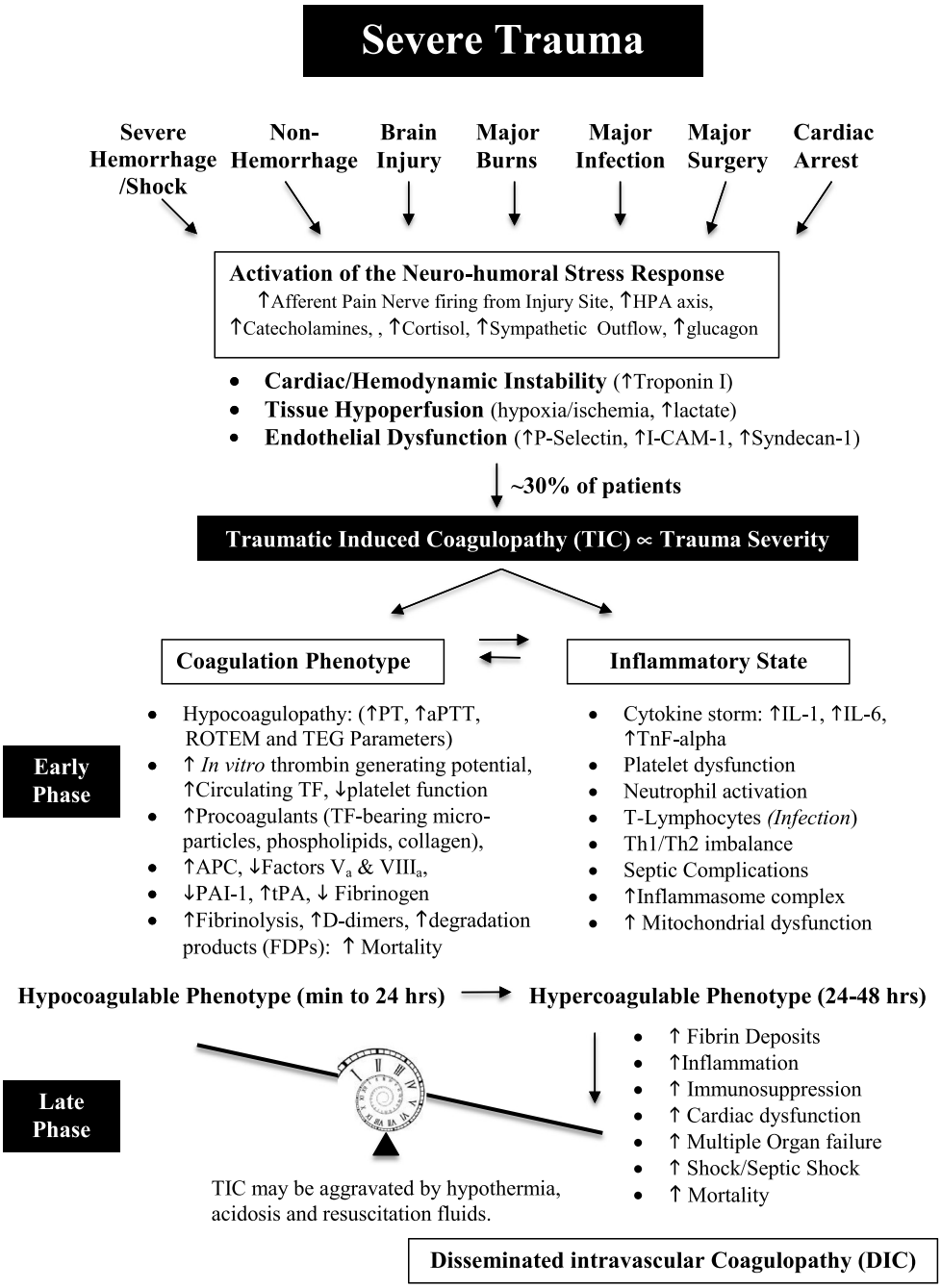

Figure 1. General scheme of TIC that occurs early after severe trauma. The upstream drivers of TIC seem to be the extent of tissue damage, hypoperfusion, and endothelial injury with different forms of trauma adding deep layers of complexity to its severity, progression, and clinical manifestation. Among the different types of trauma, severe burns exhibit the most dramatic hypermetabolic ''stress response'' of any injury. The early bleeding phenotype involves neurohormonal and cardiac/hemodynamic instabilities, leading to an imbalance among procoagulant factors, anticoagulant factors, platelets, the endothelium, inflammation, and fibrinolysis. Early TIC does not seem to be a consumptive coagulopathy but is characterized by multiple factors including prolonged clotting times, systemic anticoagulation, local factor V inhibition, a paradoxical increase in TF-initiated thrombin-generating potential, increased activated protein C, dysfibrinogenemia, impaired platelet function, red blood cells, and hyperfibrinolysis. TIC may be aggravated further by hypothermia, acidosis, and resuscitation fluids. There seems to be two phases of TIC, an early and late phase, which may evolve into DIC. Local and systemic inflammation plays an integral role in the progression of early coagulopathy. Potential biomarkers of endothelial injury include soluble P selectin (also a biomarker of platelet activation), intercellular adhesion molecule ICAM 1, and glycocalyx disruption indicator syndecan 1. Increased soluble ICAM-1 also reflects neutrophil activation and possible organ dysfunction. See text, Figure 2, and Table 1 for the major characteristics of TIC. It is important to note that specific infections (bacterial or viral) may cause distinct features in early coagulopathy.

blood ROTEM or TEG viscoelastic profiles also take approximately 60 minutes; however, clinically relevant parameters such as clot strength can be obtained within 10 minutes to guide early treatments. Fibrinolysis takes longer and is usually indicated when ROTEM or TEG maximum lysis is equal or greater than 15%;[18,22–24] however, lower percentage decreases at 30 minutes may be sensitive predictors of trauma outcomes.[25] TEG Platelet Mapping is another diagnostic method to evaluate platelet inhibition secondary to antiplatelet therapy, along with platelet aggregometry to assess platelet function. Leading trauma centers and hospitals around the world have different algorithms from which to guide patient treatment with little or no consensus on a standard-of-care assessment.[23]

What's in a Name?

> It is not to be expected that there should be agreement about the definition of anything until there is agreement about the thing itself.
>
> John Stuart Mill (1806–1873)

In the surgical and trauma literature, there seems to be a time-honored ownership about what to call early coagulopathy in trauma patients. Since the mid-1940s, a hemostatic disorder similar or analogous to TIC was reported in patients with shock, hemorrhage, burns, or cardiac arrest or those undergoing major surgery, and the condition was referred to as a *severe bleeding tendency*,[26,27] *defibrination syndrome*,[28] *consumption disorder*,[28] or in the 1970s as a *diffuse oozing coagulopathy* by surgeons treating US Vietnam combat casualties.[29] Stefanini[28] also referred to the bleeding disorder as *diffuse intravascular clotting* with fibrinolysis, which was later adopted by Gando et al.[30]

In the early 1970s, trauma surgeon Erwin Hirsch (and mentor to one of the authors A.P.C.), described the oozing-bleeding phenotype with shock he observed in Vietnam as "uniformly fatal."[31] In 1982, Moore's group named it the *bloody vicious cycle*; others called it the *lethal triad* when combined with hypothermia and acidosis, and in 2003, Brohi et al. introduced the term *acute traumatic coagulopathy* (ATC).[18,22–24] Others prefer *acute coagulopathy of trauma (ACoT)*, *acute coagulopathy of trauma/shock (ACoTs)*,[30,32] *trauma-induced coagulopathy*, or *early trauma-induced coagulopathy*.[33,34] Based on the available data, it seems timely for a global consensus on a name and acronym to reduce unnecessary confusion in the literature. TIC or ATC seem to be suitable candidates (Fig. 1).

Historical Perspective and Possible Mechanisms

> If you control hemorrhage and infection, the patient will do the recovery, since every cell in his body is working hard in that direction already. But you must understand what those cells are doing so that you can help them.
>
> Walter B. Cannon (Moore,[35] 1953, p. 816)

It is often said that there is nothing new except what has been forgotten. Nearly 70 years ago, the explanation for "the bleeding tendency" and prolonged clotting times after major surgery,[26] cardiac arrest, hemorrhage, shock, burns,[36] postpartum obstetric emergencies, pulmonary surgery, multiple fluid transfusions, and disseminated carcinoma[27] was increased fibrinolysis.[26] In 1945, Christensen and MacLeod named *plasmin* the proteolytic enzyme responsible for fibrin breakdown,[26,37] which was formed from plasminogen by tissue plasminogen activator (tPA) in the presence of fibrin. Fibrin itself was later shown to increase the catalytic efficiency of tPA by up to 100-fold.[38] In 1946, Tagnon et al.[36] further proposed that "cellular elements" from tissue damage may have contributed to early bleeding because he observed fibrinolysis in the venous blood of a few patients *before* it appeared in arterial blood, implying that some factor or factors were released into the bloodstream from the tissues. Of the 22 patients who were in shock in the study of Tagnon et al., 36% were fibrinolytic, and of those eight patients, four were hemorrhagic and three patients were hemorrhagic with severe burns.[36]

In 1946, MacFarlane and Biggs[26] summarized the field of hemostasis and proposed that a common feature underlying the different forms of trauma was shock. He wrote, "The normal function of this (hemostatic) system is at present unknown, but its activation under the conditions mentioned suggests that it may take part in the development of 'shock', and its sequelae, or in the reaction of the body to injury in general"[26] (p. 863). The prophetic words of MacFarlane and Biggs nearly 70 years ago marked a turning point in our understanding of hemostasis, and their insights exposed the multiple layers of complexity that still resonate today. In the 1980s, the early bleeding coagulopathy was understood to occur secondary to the consumption, loss, or dilution of clotting

TABLE 1. Similarities and Differences Between the DIC-Fibrinolysis and Activated Protein C Hypotheses of Early TIC

Parameter	DIC-Fibrinolysis Hypothesis	Activated Protein C Hypothesis
Occurrence at hospital admission	20–40%	20–40%
Tissue hypoperfusion	✔	✔
Endothelial dysfunction	✔	✔
Proinflammatory state	✔	✔
Prolonged clotting times	✔	✔
Consumption coagulopathy from DIC	✔	No
↑Activated protein C pathway	?	✔
↓Factors Va and VIIIa	?	✔
↑Plasma thrombin-generating potential	✔	Variable
Glycocalyx disruption	✔	✔
↓Platelet numbers	✔	Variable
↑Platelet dysfunction	✔	✔
↓Plasma fibrinogen	✔	✔
↑Plasmin levels	✔	✔
↑Fibrinolytic potential (↑tPA/PAI-1 ratio)	✔	✔
Hyperfibrinolysis (ROTEM/TEG ML > 15% within 60 min) in 15–20% of trauma patients with coagulopathy	✔	✔
• ↑D-dimers	✔	✔
• ↑Fibrin degradation products	✔	✔
DIC-fibrinolysis phenotype	Yes	No

See text for details.
ML, maximum lysis.

factors (and platelets), which was further exacerbated by acidosis and hypothermia.[39] Coagulation factors and platelets were consumed during the clot formation, lost from the intravascular compartment during bleeding, or diluted from the reversal of Starling forces and shifts of interstitial fluid into the vascular compartment after blood loss, aggressive fluid therapies (crystalloid or colloid), and blood transfusions.[23] More recent evidence suggests that coagulation changes begin at the point of injury before consumption, loss, or dilution or other traditionally presumed factors can contribute.[2,40]

The current hypotheses to explain TIC include the following: (1) the DIC-fibrinolysis hypothesis, (2) the activated protein C hypothesis, (3) the glycocalyx hypothesis, and (4) the "fibrinogen-centric" hypothesis. These hypotheses are not mutually exclusive (Figs. 1 and 2).

The DIC-fibrinolysis hypothesis proposes that the bleeding tendency is secondary to hypoperfusion/shock and endothelial injury and is associated with a prolonged PT, increased thrombin-generating potential, lower antithrombin levels, consumption of clotting factors, decreased fibrinogen, increased levels of fibrinogen degradation products (FDP), and a higher FDP/D-dimer ratio[41–44] (Table 1). The excessive increase in plasmin relative to thrombin activation is believed to fully account for hyperfibrinolysis.[42] In 2013, Hayakawa et al.[45] provided further support of the hypothesis by showing that saline infusions with low and high tissue factor (TF) could induce a DIC fibrinolytic (and fibrinogenlytic) state without tissue hypoperfusion. However, in this study, there was no measurement of tissue O_2 perfusion, and control and treatment rats seemed to be fluid overloaded (approximately 40% above normal blood volume for a 350-g rat over 4 hours) resulting in approximately 30% lower hemoglobin levels and up to threefold higher blood lactates, indicating a mismatch between tissue O_2 supply and demand. The DIC-fibrinolytic phase is followed by a DIC-thrombotic phenotype secondary to high levels of Type 1 plasminogen activator inhibitor (PAI-1) from platelets and the endothelium as well as the inhibition of fibrinolysis that may start as early as 3 hours to 4 hours after trauma and continue for 24 hours to 48 hours.[30,46,47]

The activated protein C hypothesis also proposes that bleeding occurs secondary to hypoperfusion/shock, endothelial injury, and prolonged clotting times. However, bleeding is primarily caused by activation of the endothelial protein C receptor (EPCR), thrombomodulin (TM), and TM-thrombin complex formation that favors anticoagulation by activating the protein C (APC) pathway (Fig. 2).[17,18,24] APC inhibits coagulation by inhibiting thrombin generation through proteolytic inactivation of clotting factors Va and VIIIa (enhanced by cofactor protein S) and also promotes hyperfibrinolysis by inactivating PAI-1, which leads to higher tPA, thus lowering fibrinogen and increasing FDP and D-dimer generation.[17,23] Microvascular thrombosis or DIC does not occur in this first phase with the relative sparing of platelets and fibrinogen.[43] The later prothrombotic DIC phenotype is a distinct clinical entity believed to occur after depletion of APC, clotting factors, and microvascular clot formation.[3,43] In addition to APC's antithrombotic and profibrinolytic effects, it has a number of important cytoprotective effects such as anti-inflammatory, antiapoptotic, and endothelial barrier-stabilizing properties. The protein C hypothesis is gaining clinical support from a variety of groups.[48]

The glycocalyx injury hypothesis specifically addresses the hypoperfusion/shock aspect of endothelial injury and may contribute to the DIC-fibrinolytic and activated protein C hypotheses. The hypothesis proposes a breakdown or shedding of the 0.1-μM to 1-μM-thick glycocalyx negatively charged mesh that lines and protects the luminal side of the endothelium.[43,49] Disruption of the glycocalyx, assessed by high levels of the marker syndecan 1, is believed to result in an anticoagulant state from systemic autoheparinization, which in some trauma patients can be reversed with heparinase.[43,50] Glycocalyx shedding may also be associated with a coordinated and primary signaling event that leads to further endothelial activation and follow-on coagulation and inflammatory imbalances including local thrombin formation, fibrinolysis, leukocyte, and platelet dysfunction.[50] Trauma patients with increasing injury severity and high levels of endothelial damage (syndecan 1) show prolonged aPTT, high sympathoadrenal activity, protein C depletion, elevated soluble TM, hyperfibrinolysis, and inflammation.[24,43] It is interesting to note that in the early 1960s, Willoughby[51] diagnosed a small number of catastrophic postpartum hemorrhage cases as having "heparinemia" not "defibrination syndrome," and today, it is tempting to speculate that these early bleeding states may have involved widespread endothelial damage, supporting the glycocalyx hypothesis.

The fibrinogen-centric hypothesis is an older hypothesis with its roots dating back to the mid-1940s and is attracting a groundswell of clinical interest today in trauma,[52,53] postpartum hemorrhage, and cardiovascular surgery.[54,55] The hypothesis focuses on the loss of fibrinogen as the primary driver of TIC, resulting in a reduction in viscoelastic clot amplitudes, high FDPs, and D-dimers.[52,53,56] Acute traumatic hypofibrinogenemia occurs when the rate of fibrinogen breakdown is greater than its in vivo synthesis and the degree of fibrinogen loss is dependent on the severity of trauma, shock, and fluid therapies.[52,53,56] Lower fibrinogen may also alter platelet function and increase protein C activation on the EPCR-TM-thrombin complex and exacerbate the bleeding phenotype[12] (Fig. 2). Current replacement therapies to correct the defect include high levels of fibrinogen concentrate or cryoprecipitate along with antifibrinolytics to reduce bleeding.[52,53,57]

The Thrombin "Paradox" and Its Clinical Relevance to TIC

> Reconstituted systems are as realistic as our insight into the clotting mechanism allows: extrapolation to physiology should therefore be regarded with due suspicion.
>
> Hemker et al.[58] (2004, p. 171).

A common observation in a majority of TIC patients is a paradoxical increase in plasma thrombin-generating potential in vitro compared with healthy individuals,[59] with higher values correlating with injury severity.[60–62] The increases may be caused by higher plasma levels of TF, TF-bearing microparticles, procoagulant phospholipids, or lower fibrinogen associated with widespread endothelial dysfunction (Fig. 1); however, they are not sufficient by themselves to represent a clinically relevant thrombotic state in vivo.

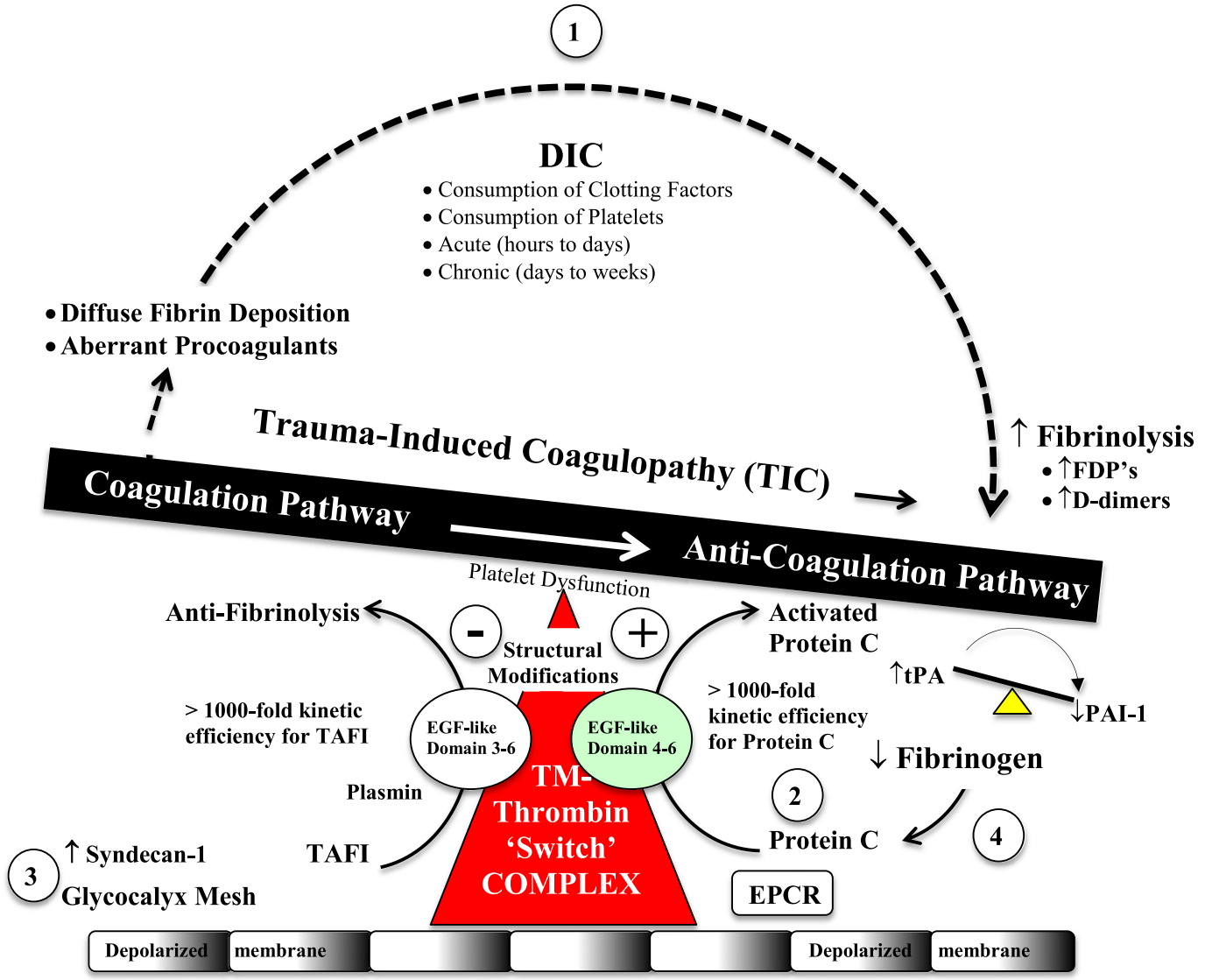

Figure 2. Broad schematic of the four TIC hypotheses and the TM-thrombin switch mechanism of hemostatic regulation. The current hypotheses to explain TIC include (1) the DIC-fibrinolysis hypothesis, (2) the activated protein C hypothesis, (3) the glycocalyx hypothesis, and (4) the fibrinogen-centric hypothesis (see text). Central to the in vivo regulation of coagulation is the state of the endothelial TM-thrombin complex, which can either activate protein C anticoagulant or TAFI coagulation pathways. The switch may involve structural or posttranslational covalent modifications at the different sites on the TM-thrombin complex, which bind and activate protein C or TAFI in the presence of their respective cofactors and/or receptors.[8] The TM luminal stalk has an outer *N*-terminal C-lectin–like domain, a longer middle section built of endothelial growth factor (EGF)–like repeats, and a shorter lower serine-rich segment. The EGF-like 5 and 6 domain contains high-affinity sites for thrombin, and the lower serine-rich segment has low-affinity sites for thrombin, and sites for platelet factor 4 (PF4) binding. Activation of protein C is believed to occur within the EGF-like domains 4 to 6 and TAFI within EGF-like domains 3 to 6, which has 13 more residues than the protein C domains.[9,10] Protein C activation on TM-thrombin is further accelerated through binding to EPCR. Other regulatory factors may involve changes to (i) the polymerization-depolymerization of actin within the glycocalyx, which can modulate permeability, vascular tone, innate immunity, and leukocyte adhesion; (ii) the extent of endothelial membrane depolarization from changes in injury ionic currents; (iii) platelet dysfunction; and (iv) inflammatory cytokine balance.[11] Endothelial cells are also a source of circulating tPA and its inhibitor (PAI-1), prothrombotic phospholipids, microparticles, and anticoagulants. Díez et al.[12] further reported an inverse relationship between fibrinogen levels and activated protein C and proposed that at high levels, fibrinogen would inhibit TM-thrombin activation of protein C and, at low levels, would activate protein C activation and worsen the bleeding phenotype.[12] DIC is separate from early TIC because it involves aberrant procoagulants and intravascular fibrin deposits (see text).

In 2009, Dunbar and Chandler[63] also reported an increase in the thrombin generation potential in trauma patients, and others such as Gando et al.[30,46] have interpreted their data as supporting evidence for a DIC phenotype. We argue that it is premature to draw this conclusion based on an in vitro thrombin generation reconstituted system, which is platelet poor and does not capture the effects of flow and shear stress.[19,58] In addition, clotting occurs at the end of a lag time when a tiny thrombin "burst" occurs and when more than 95% of all thrombin is still to be formed.[58] The paradox between higher thrombin-generating potentials in patients with a TIC bleeding-oozing phenotype may be partially explained from thrombin itself being a poor activator of protein C or TAFI pathways in vitro compared with the more clinically relevant TM-thrombin complex, which can activate both pathways approximately 1,000-times faster than free thrombin.[9,10,64] Currently in vitro assays cannot separate the free versus bound contributions of thrombin to coagulopathy in vivo. Loss of antithrombin III also contributes to the elevated thrombin levels seen in vitro and may have direct effects on clotting kinetics and localization.[63,65]

In addition, in 2015, Carlier et al.[20] concluded that the thrombin generation test was too variable to be a useful diagnostic tool in their sepsis patients with or without DIC. The rate index of the propagation phase of thrombin generation and lag time for thrombin generation in their DIC patients did not differ from healthy subjects.[20] Similarly, in 2014, Cardenas et al.[59] reported wide thrombin-generating variability in a trauma population, with a subgroup of patients suffering minor injuries having profound increases in thrombin-generating capacity, and another group, with more severe injuries, including shock, showing no consistent trends. While thrombin capacity and kinetic tests have clinical utility to discriminate patients with hemophilia, antithrombin III deficiency, and lupus anticoagulant,[20] they seem to be problematic in trauma patients to predict or guide treatment of acute coagulopathy.

Where Do We Stand Today?

> What we anticipate seldom occurs; what we least expect generally happens.
>
> Benjamin Disraeli (1804–81), *Henrietta Temple*

In our view, TIC is a dynamic entity that evolves over time, and no single hypothesis explains the different manifestations of the coagulopathy. However, early TIC is not DIC because an increased in vitro thrombin-generating potential and/or fibrin and fibrin degradation products, while suggestive of DIC, does not confirm a clinically relevant prothrombotic state in vivo. To be clear, we are not dismissing "DIC with a fibrinolytic phenotype"; we are disagreeing with its conceptual framework and historical basis. If there is no evidence of diffuse anatomopathologic intravascular fibrin deposition, it is not a DIC, and the "DIC hypothesis with a fibrinolytic phenotype" is a confusion of terms and should be abandoned. We suggest that a state in which fibrinolytic activity exceeds the capacity of the hemostatic system to make stable clots, resulting in excess or uncontrolled hemorrhage, be termed *systemic activation of lysis with poor hemostasis*. While fibrinolysis plays a role in TIC, it is interesting to note that we recently showed in the rat model of hemorrhagic shock that small-volume 7.5% NaCl adenosine, lidocaine, and Mg^{2+} (ALM) reversed TIC in 5 minutes after an intravenous bolus demonstrating that clotting factors, postshock platelets, and coagulation pathways were fully operational at this time.[66] Such a rapid reversal after 20-minute bleed and 60-minute shock implies that early TIC in this model was not a DIC-consumptive coagulopathy, although some consumption must have occurred.[66] A distinguishing feature separating TIC from DIC is disseminated intravascular fibrin deposition (Fig. 2). In a recent prospective cohort study, Rizoli et al.[67] concluded that severely injured patients who had DIC scores suggestive of DIC within 24 hours of trauma did not possess DIC based on pathologic findings. The authors concluded that DIC is exceptionally uncommon in the severely injured and that the ISTH [International Society for Thrombosis and Hemostasis] scores are not a reliable prognostic indicator of DIC.[67] The score uses a five-step diagnostic algorithm to calculate a DIC coagulopathy.[23] As the field of coagulopathy advances, DIC is becoming increasingly harder to diagnose and new in vitro methods and biomarkers are required to guide therapy.[68]

The activated protein C hypothesis has many attractive features to explain TIC. However, the underlying mechanisms remain unclear because only modest increases in APC are found in TIC patients, making it unlikely to be the sole determinant or activator.[69] Furthermore, a central tenet of this hypothesis is that APC causes a systemic anticoagulation through inactivation of factor Va and factor VIIIa. This is difficult to reconcile with the increase in thrombin generation observed in TIC patients on admission to hospital. It is possible, however, that APC is critical to the evolution of TIC over time.

The glycocalyx hypothesis is appealing as it addresses widespread endothelial injury, and recent data suggest that it may be reversible over short time frames, making it a potentially valuable drug target.[70] However, in addition to changes in syndecan 1, the hypothesis needs to be validated with direct investigations using intravital microscopy, electron microscopy, or confocal microscopy.[71] Recent data using intravital microscopy add support to this hypothesis.[72]

The fibrinogen-centric hypothesis is clinically relevant, particularly in moderate-to-severe hemorrhage and shock states. However, as with the APC hypothesis, many questions remain on how to link bleeding to mechanisms such as the timing of fibrinogen depletion, the roles of FDP and soluble fibrin monomer, and the contribution of possible deficits in fibrin cross-linking by factor XIII. Fibrinogen concentrates do have the advantage of reducing the need for ratio-driven transfusion of allogenic blood products, and fibrinogen replacement therapy, combined with fresh frozen plasma, other plasma products, or coagulation factor concentrates (e.g., prothrombin complex concentrate, and recombinant factor VIIa) are being explored as therapeutic strategies.[57] Despite enormous advances in the last decade, a potential shortfall in the current set of hypotheses of TIC is that they ignore the subtleties of platelet and red blood cell numbers and function to assess and treat the disorder.[23,73] Further animal models in different trauma states are required to investigate the underlying mechanisms, and prospective randomized controlled trials are urgently needed.

In conclusion, although the underlying mechanisms of TIC are not well understood, the major drivers seem to be tissue hypoperfusion, endothelial injury, and inflammation, with the different types of trauma adding deep layers of complexity to its severity, progression, and clinical manifestation (Figs. 1 and 2, Table 1). Although various names for this bleeding phenotype have been proposed, the available evidence suggests that broadly, at least two phases exist over time, which could be grouped together as TIC. The early acute phase covering the period from point of injury to postresuscitation and initial surgery (up to perhaps 24 hours) could reasonably be assigned a nomenclature of ATC. Further advances in clarifying taxonomy will be made with new diagnostic tools to unravel the underlying etiology and new drugs that target endothelial injury or other aspects of pathophysiology. It is a sobering thought when considering TIC and the crosstalk between coagulation and inflammation that there are an estimated 100,000 TM molecules[9] and up to 20,000,000 annexin II molecules (which bind tPA and plasminogen) located on each of the 10^{13} endothelial cells lining all blood and lymphatic vessels[74] within the body covering a surface area of 3,000 to 7,000 m^2 (up to the size of an NFL football field!).[75,76] The endothelial TM-thrombin complex and fibrinolytic system are attractive drug targets because they can "switch" from a fibrinolytic to antifibrinolytic phenotype, and vice versa, in seconds to minutes, as shown with the use of clot-busting agents such as alteplase or antifibrinolytic tranexamic acid.[77] Finding the right balance in restoring homeostasis in vivo remains the ongoing challenge in the diagnosis and treatment of early coagulopathy following trauma.

AUTHORSHIP

All authors contributed equally to the design, implementation, literature analysis, and writing of the manuscript.

DISCLOSURE

F.R.S. and A.P.C. are military service members. This work was prepared as part of their official duties. Title 17 USC §105 provides that ''copyright protection under this title is not available for any work of the US Government.'' Title 17 USC §101 defines a US Government work as a work prepared by a military service member or employee of the US Government as part of that person's official duties.

G.P.D. is the sole inventor of the ALM concept for cardioplegia, surgery, infection, and trauma. H.L.L. and R.S. have no conflicts to declare.

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