Trauma Induced Coagulopathy

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Foreword

The absence of hemorrhage control identified as "trauma-induced coagulopathy" is a major contributor to mortality following potentially survivable trauma. This comprehensive and timely text integrates reviews on the biology of blood coagulation, including the plasmin–fibrin/fibrinolysis system, by describing human and animal studies of trauma-induced coagulopathy. These latter studies describe the role of platelets, the endothelium, the fibrinolytic system, the complement system, and inflammation, as well as recent discoveries associated with damage-associated molecular pattern molecules (DAMP) in both hemostatic and thrombotic pathology.

These reviews are linked to practical descriptions of those technologies presently available for assessing trauma-induced coagulopathy in clinical scenarios and also summarize their limitations. The most current clinical studies describing the therapeutic intervention trials with red blood cells, platelets, cryoprecipitate, whole plasma, and plasma derivatives, as well as current concepts regarding antifibrinolytic agents are summarized. The hypercoagulable state seen following successful attenuation of bleeding after injury, which is either associated with the primary injury or a consequence of those therapies used to treat the original pathology, is also discussed in detail.

While no surrogate for human pathology in the study of trauma is completely adequate, both the animal models and numerical modeling procedures described in this monograph have been advanced as mechanisms for the transition of laboratory-based hypotheses to the evaluation and therapeutic intervention associated with trauma.

This book provides a catalyst to link laboratory research-based assets with the clinical expertise of surgeons and physicians. This interaction should yield the comprehensive studies required to develop therapeutic and diagnostic techniques to thoroughly understand and effectively treat trauma-induced coagulopathy.

Burlington, VT — Kenneth G. Mann

Preface

Like many good ideas in clinical medicine, trauma-induced coagulopathy was the product of a routine multidisciplinary research meeting. Two research fellows, Eduardo and Hunter, were presenting their experimental plans and remarked that their study backgrounds were based on literature from a variety of disciplines in diverse journals. They proposed compiling a collection of seminal papers from the experts in the field to assist those interested in coagulation research. The idea was further stimulated by frequent questions from our colleagues on the surgical intensive care unit rounds who wanted to understand the basis for our new concepts in coagulation management that were not available in surgical texts. As the process unfolded, it became clear that multiple classic papers were required for each concept. The collection soon became too large for practical distribution, and the next evolutionary step was to extract information from each contribution to generate a reference handbook. We ultimately recognized that the individual components of the coagulation system were simply too complex to relegate to a summary in a handbook. Thus, we agreed the most useful reference would be a text of chapters written by those conducting research in various fields related to coagulation.

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Historical Perspective of Trauma Induced Coagulopathy

Keywords

History
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Plasmin
Platelets
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Thrombelastography
Thromboelastometry

Injury is the second leading cause of death worldwide [1], and the third leading cause of mortality in the United States [2]. Despite advances in emergency medical systems and trauma care, deaths from injury have increased in the United States over the last decade [3]. In both the civilian [4] and military [5] settings, uncontrolled hemorrhage is the leading cause of preventable death after injury. In civilian studies, 80 % of deaths from hemorrhage occur within the first 24 h, at a median time of 2 h [4]. Consequently, there is intense interest worldwide in the pathogenesis of coagulopathic bleeding after injury and its early management. While there have been substantial insights, the words of Mario Stefanini in his address to the New York Academy of Medicine in 1954 [6] remain applicable today: "The ponderous literature on the subject of hemostasis could perhaps be considered a classical example of the infinite ability of the human mind for abstract speculation. For several years, the number of working theories of the hemostatic mechanisms greatly exceeded and not always respected the confirmed experimental facts. In recent years, however, the revived interest in this field has led to an accumulation of new findings, which has been almost too rapid for their orderly incorporation into a logical working pattern. As a result, we have rapidly gone from a state of orderly ignorance to one of confused enlightenment, from which we have not emerged as yet."

The evolution of our understanding of the complexities of coagulopathy associated with trauma has been, in large part, the result of collaboration between civilian and military researchers and clinicians. The earliest reports

of coagulopathy in injured patients were generated from military research teams, often including civilian consultants, during major wars. These novel observations would then intensify hemostasis research in civilian centers. Ultimately, the resulting findings improved coagulopathy management in subsequent conflicts, and primed the environment for making new observations. The specific contributions to our understanding of coagulopathy, however, are somewhat difficult to ascertain from World War I through Vietnam because the primary focus was on optimizing shock resuscitation at a time when plasma or whole blood was employed to replace acute blood loss [7]. Nonetheless, several landmark contributions are well recognized.

In 1916 the US National Research Council formed a Subcommittee on Traumatic Shock that collaborated with the British Medical Research Committee to study wounded soldiers in the front lines of France. Among them was Walton B. Cannon from Harvard, who was perplexed by the inconsistencies of the prevailing toxin theory of shock. Based on observations made on the battlefield in France during 1918 [8], Cannon wrote "…the heart, nervous system and other organs are suffering from an insufficient blood supply" and later admonished "if the pressure is raised before the surgeon is ready…blood that is sorely needed may be lost." Cannon documented experimentally that stress, i.e., epinephrine infusion into animals, provoked hypercoagulability followed by hypocoagulability [9]. Cannon also stated prophetically "…shock is a loss of homeostasis, and without homeostasis the patient does not survive." In 1936, based on Cannon's observations and his own research at Vanderbilt and Johns Hopkins, Alfred Blalock [10] concluded "the work of recent years has shown that shock is dependent on an inadequate supply of blood to the tissues, which may be brought about by the most diverse causes," i.e., hematogenic, neurogenic, vasogenic, and cardiogenic.

In the spring of 1940, with major victories established by Germany and Japan, the US involvement in the war appeared inevitable. Military experts recognized that bottled whole blood would be logistically impractical and enlisted the expertise of Edwin Cohen, a Harvard biochemist, to deconstruct blood in order to deliver its components to the battlefield [11]. Cohen was successful in purifying albumin as well as preparing plasma. At the onset of World War II, the National Research Council's Committee on Transfusion recommended that dried plasma—not blood—would be used if combat occurred outside the continental United States because it was easy to prepare and transport, whereas whole blood had to be typed, cross-matched, and refrigerated. Based on the legendary work of consultant Edward D. Churchill [12] in North Africa, who concluded, "wound shock is blood volume loss," the policy was changed to whole blood administration and implemented in Italy in 1943.

In 1952, the Board for the Study of the Severely Wounded systematically reviewed the cause of death in 186 war casualties. The report was dominated by the discovery of a new syndrome "post-traumatic renal failure" that was attributed to prolonged hypoperfusion. This observation ultimately led to a paradigm shift in resuscitation, incorporating crystalloid as a fundamental component of initial fluid administration [13]. Contemporary studies in civilian hospitals, based on observations in trauma and burn patients, reported a "severe bleeding tendency" implicating fibrinolysis [14, 15]. The plasmin–antiplasmin system had been well characterized at this point [16]. Alternatively,

others postulated the loss of a labile clotting factor in whole blood and recognized the key role of platelets in hemostasis [17, 18]. In 1954, Stefanini [6] noted that postinjury hemorrhage persisting despite surgical control of bleeding was variously referred to as medical bleeding, diffuse bleeding diathesis, post-transfusion bleeding disorder, and disseminated intravascular coagulation (DIC), reflecting a general lack of consensus in the pathophysiology.

During the Korean War, William Stone is credited with promoting Surgical Research Teams in the combat zone in Korea [19]. Scott and Crosby [20], representing one such team, reported that the prothrombin time (PT) was doubled in combat casualties while platelet count and fibrinogen were increased. They also speculated that the cause was due to a labile clotting factor during blood storage. Artz and Fitts [21] observed that severely injured soldiers in the Korean Conflict required both return of shed blood and crystalloid for optimal survival, inspiring the later seminal work of Tom Shires [22] defining the scientific basis for crystalloids.

After the Korean War, civilian studies implicated a number of causative factors responsible for bleeding associated with major surgery requiring transfusion, including DIC [23], fibrinolysis [24], compromised viability of platelets in stored blood [25], and the loss of the labile factors V and VIII during storage [26]. The initial response to experimental hemorrhagic shock was hypercoagulability, followed by a progressive state of hypocoagulability with decreases in factors V, VIII, IX, X, and XI along with reduced fibrinogen and platelets [27]. The early clinical studies in Baltimore further identified a third phase of hypercoagulability in those who survived the intermediate period of hypocoagulability [28]. The authors concluded that in surviving patients, the oscillatory pattern converges into a "dynamic homeostatic state," whereas, in non-survivors, "fluctuations exceeded safe limits and behaved like a runaway system."

Based on the compelling experimental work by Shires et al. [22], the major change in resuscitation strategy in Vietnam was the administration of large volumes of crystalloid. This policy virtually eliminated acute kidney dysfunction, but led to a new entity coined "Da Nang Lung" [29], later termed the acute respiratory distress syndrome (ARDS) as the civilian counterpart [30]. The first large study on coagulation disorders in combat casualties from Vietnam was reported by Simmons et al. [31]. In their comprehensive analysis of 244 injured soldiers, the authors concluded that there is "an initial phase of hypercoagulability followed by hypocoagulability and this seemed best explained by DIC. "Massive transfusion was accompanied by a dilutional coagulopathy compatible with factor levels in stored blood. Platelet levels fell, but PT, partial thromboplastin time (PTT), and fibrinogen levels were less affected. "Fresh whole blood partially counteracts this dilutional state, but is rarely necessary," concluded Simmons. Miller et al. [32] studied 21 patients requiring a massive transfusion in Vietnam. Significant coagulation defects were not evident until 20 units of stored blood were administered. A dilutional defect in platelets appeared to be the primary cause for bleeding, and this was reversed with fresh whole blood administration. Interestingly, they reported no evidence of DIC or fibrinolysis. In 1974, John A. Collins [33] systematically reviewed the problems associated with massive transfusion and offered these observations: [1] "Early complete replacement of

blood volume in the massively bleeding patient lessens the impact of exchange transfusion with stored blood," [2] "An intact circulation is a very good defense against the metabolic problems of massive transfusion," and [3] "Historically as new problems associated with massive transfusion have been defined, they have almost always been grossly overstated."

Coagulation research in civilian institutions in the early 1970s began to elucidate the molecular events resulting in thrombin generation as the common end product of the extrinsic and intrinsic clotting pathways [34, 35]. In the clinical arena, trauma surgeons recognized that controlling bleeding from the liver was a priority to improve survival following trauma, but much of the work concentrated on techniques to achieve mechanical hemostasis with some mention of packing when bleeding continued [36–38]. It was also noted that tissue disruption from blunt trauma appeared to be associated with more problematic bleeding than penetrating wounds, stimulating resurgent interest in DIC and subsequent pulmonary microemboli [39, 40]. In the later 1970s, trauma surgeons began to recognize that bleeding following massive transfusion with stored blood required supplemental clotting factors. This literature is confounded by the fact that blood banks began to implement blood component therapy [41], a policy change that unmasked the prevalence of a trauma-related coagulopathy. In 1979, our group [42] and others [43–45] observed that the majority of patients succumbing to liver injuries died of a coagulopathy, after surgical control of bleeding. We recommended pre-emptive fresh frozen plasma (FFP): "If the patients remain hypotensive after the second unit of blood, FFP should be administered then and with every fourth unit thereafter." Furthermore, we advocated fresh whole blood "…if bleeding persists despite normal PT, PTT, and bleeding times" [42]. Stimulated by these findings, we analyzed a group of patients who developed life-threatening coagulopathy with major vascular injuries and noted the compelling association of metabolic acidosis and hypothermia. Confirming the independent effects of acidosis and hypothermia on coagulation experimentally [46], we proposed the "bloody vicious cycle" in 1982 [47], which subsequently became known as the "lethal triad" and now is often referred to as "resuscitation-associated coagulopathy." The concept of truncating definitive repair of all injuries in coagulopathic patients in the operating room, to allow for correction of hypothermia, acidosis, and coagulopathy in the intensive care unit, was the fundamental basis of "damage control surgery" introduced by Harlan Stone et al. in 1983 [48]. In studying our coagulopathic injured patients in 1982 [47], we noted that higher ratios of FFP to stored blood were associated with improved survival and advocated presumptive FFP:blood administration of 1:4 in the emergency department. Charles Lucas and Anna Ledgerwood also conducted animal work that supported the concept of pre-emptive FFP during massive transfusion [49]. In the later 1980s [50], the Detroit General Group systematically studied coagulation abnormalities in patients requiring a massive transfusion of stored red blood cells (RBC) and postulated them to be secondary to consumption of factors, reflected in standard measures of coagulopathy, i.e., PT, PTT, and thrombin time (TT). Collectively, the coagulopathy associated with severe trauma was postulated to be secondary to both consumption and dilution of clotting factors. There was also considerable inter-

est in the early administration of platelets due to the long-term observation of deteriorating platelet numbers in stored blood, although clinical trials failed to confirm a benefit of pre-emptive platelet administration [51].

In the ensuing decade much of the clinical investigation centered on optimizing the use of damage control surgery for refractory coagulopathy [52–54]. Coagulation research during this period was further complicated by the practice of aggressive crystalloid resuscitation targeting supra-physiologic oxygen delivery, promulgated by William Shoemaker et al. [55]. This resulted in an epidemic of compartment syndromes, with much attention diverted to the urgent need to decompress the abdomen following protracted shock that required high volume crystalloid resuscitation [56]. In retrospect, most of the compartment syndromes and, to a significant extent, coagulopathies were generated by overzealous infusion of crystalloid driven by the subsequently disproven concept of supra-physiologic oxygen delivery [57]. There is no question that chasing oxygen delivery with Swan-Ganz catheters and attempting to correct metabolic acidosis with large volume crystalloid loading added a substantial component of dilutional coagulopathy [58].

The first decade of the twenty-first century perhaps represents the most significant insights gained into trauma-associated coagulopathy in modern history, and many of these investigators responsible are authors in this monograph. Progress was unquestionably inspired by the revolutionary concept of the cell-based model of coagulation proposed by Hoffman and Monroe [59] who emphasized the fundamental role of platelets as a platform for clotting factor assembly and thrombin generation on damaged endothelium. Paradoxically, these new insights led to the unbridled use of activated factor VII, which was ultimately proven unjustified [60, 61]. In 2003, MacLeod et al. [62] from the University of Miami made the observation that 28 % of severely injured patients had an elevated PT on arrival to the hospital, and this was associated with an increased risk of mortality. At the same time, Karim Brohi [63] from the Royal London Hospital reported that 24 % of severely injured patients had prolonged clotting times, and extended their analysis to demonstrate this abnormality was independent of fluid administration and, consequently, termed the syndrome the “acute coagulopathy of trauma” (ACOT). Stimulated by his observations on the ACOT in London, Brohi pursued a trauma research fellowship with Mitch Cohen and colleagues in San Francisco. Together, in 2007, this civilian research team provided compelling evidence that activation of protein C is an integral component of ACOT [64]. Shortly thereafter, Par Johansson [65] from Copenhagen added evidence of endothelial glycocalyx degradation, stimulating interest in the endotheliopathy of ACOT. Additional evidence has implicated the innate immune response in general [66], and neutrophils specifically [67] in the pathogenesis of ACOT.

Simultaneous with these provocative studies in civilian trauma centers, the military recognized coagulopathy as the most common source of preventable death in soldiers in the war in Iraq [68]. When confronted with this challenge, Hess and colleagues from the US Army [69] suggested the best solution was to replace the acute blood loss with a blood component formula that would replicate the whole blood lost, thus the genesis of the 1:1:1 concept. In 2007, Borgman et al. [70] reported the US military experience in Iraq suggesting a

survival benefit for soldiers resuscitated with an FFP:RBC ratio approaching 1:1 when they required a massive transfusion (10 units of red blood cells (RBC) in 24 h). This report was extrapolated to support the proposed "damage control resuscitation" concept with 1:1:1 as the centerpiece. Although the relative simplicity of this recommendation is appealing, this concept is not intuitively scientific and has prompted vigorous debate that continues today [71–74]. Ultimately these debates stimulated the National Institutes of Health (NIH) to conduct a Trans-Agency Coagulopathy in Trauma Workshop, held in Bethesda in April 2010. Out of this meeting came the consensus that the term "trauma-induced coagulopathy" (TIC) would be employed to describe what was previously referred to as ACOT.

Conspicuous among the many questions is whether platelets should be given empirically with the initial administration of FFP and RBC units in patients at risk for TIC. In contrast to platelets and plasma for first-line therapy in the United States, the European approach has been to load fibrinogen [75]. The current limitation in assessing platelet function for hemostasis has hampered resolution of this topic [76, 77]. Further is the debate of the optimal ratio of FFP:RBC units in the patient at risk for TIC. The only randomized trial to date failed to demonstrate a survival advantage of a 1:1 versus 1:2 FFP:RBC ratio when delivered with platelets [78, 79].

The role of systemic fibrinolysis in TIC has added another layer of controversy, which was largely overlooked until the widespread implementation of global viscoelastic assays of hemostasis in trauma care, such as thrombelastography (TEG) and thromboelastometry (ROTEM) [80–83]. Unfortunately, the CRASH-2 trial reported in 2010 [84] prompted indiscriminate use of tranexamic acid (TXA), until the limitations of this study were recognized [85, 86]. Subsequently, it was generally acknowledged in the United States that TXA should be reserved for selected populations until randomized trials clarify the indications, including its role in traumatic brain injury patients. Recently the elucidation of early fibrinolysis shutdown [87] has added to the concern of routine TXA administration. Finally, the issue of whether goal-directed therapy via viscoelastic assays such as TEG or ROTEM is superior to a fixed ratio approach is ongoing. A large retrospective study indicated that TEG-driven resuscitation was more effective than 1:1:1 approach [88], and our recent single-institution randomized study [89] indicated that TEG was more effective in guiding a massive transfusion protocol than conventional laboratory tests (PT, PTT, platelet count, and D-dimers). In 2013, driven by these ongoing controversies, the NIH funded a Trans-Agency Research Consortium for Trauma-Induced Coagulopathy (TACTIC) in collaboration with the Department of Defense (DOD) with the aim of elucidating the underlying mechanisms of TIC from "road to rehabilitation."

In sum, the need to define the scientific basis for blood component administration and regulation of fibrinolysis in the critically injured patient is as clear today as it was 60 years ago and, as optimistically articulated by Mario Stefanini [6], we are making substantive progress. "While the multiplicity of hypotheses and the conflict of experimental findings still deny us a firm theoretical basis for the interpretation of the mechanisms of hemostasis, the impact of the advances of the last 10 years on the diagnosis and management

of the bleeding patient has been staggering. New diagnostic tests have greatly increased the accuracy of the diagnosis; broader interest in the isolation of coagulation factors and of platelets points to more specific methods of treatment in the near future. One feels that, with the unending ferment of ideas and fervor of investigation in this field, great progress lies ahead."

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