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Hemodilution is Not Critical in the Pathogenesis of the Acute Coagulopathy of Trauma[1]

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Background. **The acute coagulopathy of trauma is multifactorial, but generally believed to be aggravated by coexisting acidosis, hypothermia, and hemodilution. While acidosis and hypothermia have been extensively evaluated, there is a paucity of data on the independent role of hemodilution in this scenario. We therefore hypothesized that hemodilution will impair coagulation following experimental trauma and hemorrhagic shock.**

Methods. **Adult male Spraque-Dawley rats underwent trauma and hemorrhagic shock, followed by resuscitation with 2 × SBV using normal saline (NS). Thrombelastography (TEG) was performed before and after shock.**

Results. **In this trauma model, resuscitation resulted in a hemodilution of 50% (43% ± 4.05% *versus* 19.8% ± 3.96% Hct pre-shock *versus* post-shock , $P < 0.0001$). Despite the substantial hemodilution, there was no significant change in clot strength (12.96 ± 2.84 *versus* 11.79 ± 1.28 dynes/cm^2 G pre-shock *versus* post-shock, $P = 0.13$). Similarly, the onset of coagulation (R time) was not impaired (1.68 ± 1.74 s *versus* 1.75 ± 0.63 s R time pre-shock *versus* post-shock, $P = 0.45$).**

Conclusion. **In the absence of hypothermia and acidosis, hemodilution (≤50%) has a trivial effect on coagulation following trauma and hemorrhagic shock. These data call to question the commonly held belief that hemodilution *per se* is critical in the development of post-injury coagulopathy.** © 2012 Elsevier Inc. All rights reserved.

Key Words: **blood coagulation disorders; coagulation; coagulopathy; acute coagulopathy of trauma; hemorrhagic shock; transfusion; massive transfusion; hemodilution; dilutional coagulopathy; resuscitation; critical care; crystalloid.**

INTRODUCTION

Beginning with the discovery that post-injury shock was caused by acute blood loss [1] research has continued in its endeavor to optimize resuscitation strategies. In World War II, whole blood transfusion was finally accepted as beneficial for resuscitation of traumatic shock [2, 3]. With the discovery of ABO blood groups [4], blood component separation [5], and storage [6], initial investigation focused on replacement of these components following massive transfusion [7]. As a result, much of the emphasis on the coagulopathy following life threatening injury was attributed to the dilution of clotting factors as a result of component therapy [8]. In fact, avoiding hemodilution formed the basis for hypotensive resuscitation, i.e., the dual benefit of avoiding blood pressure dislodgement of a hemostatic plug and hemodilution that would provoke a coagulopathy [9]. For the past 30 y, contributions of physiologic derangements, beyond plasma clotting factors, added a further dimension to the investigative process, notably the bloody vicious cycle emphasizing the role of coexisting hypothermia and acidosis [10, 11]. It is believed that the acute coagulopathy of trauma is multifactorial; aggravated by coexisting acidosis, hypothermia, and hemodilution. While the independent contributions of acidosis and hypothermia have been extensively evaluated, there is a paucity of data on

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the independent role of hemodilution in this scenario. Traditionally, evaluation and treatment of post-injury coagulopathy has been based largely on the platelet-poor plasma assessment of the extrinsic pathway (prothrombin time, PT) and the intrinsic contact pathway (activated partial thromboplastin time, aPTT). These tests, however, reflect <5% of the thrombin generated during clot formation [12]. Previous clinical studies have shown that up to 35% of the variability in the INR and 20% of the variability of the PTT are unrelated to underlying clotting factor levels [7]. For the past decade, coagulation research has been redirected based on the cell-model of hemostasis, recognizing the central role of platelets, the endothelium, and their interaction with the plasma elements [13]. Thrombelastography (TEG), employed in liver transplant [14] and cardiac surgery[15] for half a century, has recently been applied to the trauma setting, facilitated by the modification of provoking coagulation with tissue factor, i.e., the rapid TEG. Additionally, TEG has been shown to be superior to PTT and INR in detecting clinically relevant clotting abnormalities following experimental trauma and hemorrhagic shock [16]. We therefore hypothesized that hemodilution has an independent effect on the acute coagulopathy of trauma, using TEG as a comprehensive assessment of clot integrity.

MATERIALS AND METHODS

All reagents were purchased from Sigma-Aldrich Corp. (St. Louis, MO) unless otherwise specified. Thrombelastography equipment and supplies were obtained from Haemonetics Corporation (Niles, IL); 0.9% injection grade normal saline (NS) was purchased from Baxter Healthcare (Deerfield, IL); iSTAT equipment and supplies were purchased from Abbott Laboratories (Abbott Point of Care, Princeton, NJ). Polyethylene tubing was acquired from Fisher Scientific (Pittsburgh, PA). No heparin was given in this study.

Trauma Model

Adult male Sprague-Dawley rats (Harlan Laboratories, Indianapolis, IN) weighing 350–450 g were housed under barrier-sustained conditions and allowed free access to food and water before use. All animals were maintained in accordance with the recommendations of the Guide for the Care and Use of Laboratory Animals, and this study was approved by the University of Colorado Health Sciences Center Animal Care and Use Committee. Animals ($n = 10$) were anesthetized with inhaled isoflurane, and a cardiac puncture was performed to collect a blood sample for a pre-shock TEG. The femoral artery and vein were then cannulated with polyethylene (PE-50) tubing for continuous invasive pressure monitoring and to establish venous access for resuscitation. A tracheotomy was performed, at which point the animal was placed on 40% 0_2 using an air-oxygen mixer (Sechrist, Anaheim, CA) at a flow rate of 2 L per min. After a 45-min observation period, a laparotomy was performed to simulate tissue injury, and hemorrhagic shock was induced over a period of 10-min through the arterial catheter to maintain a mean arterial pressure (MAP) of 35 mmHg for 30 min. NS was infused at a rate of 0.4 mL/h to maintain patency of the femoral arterial line during shock. At the end of shock, animals were resuscitated with 2 × shed blood volume in NS over a 30-min period. Animals were then observed for 1.5 h following resuscitation. TEG was performed at baseline, and at the completion of the experiment, 120 min post-shock. Euthermia was maintained throughout the experiment with the use of a heat lamp. Pre-shock and post-shock arterial blood gas measurements were performed to confirm the absence of metabolic acidosis, as well as pre-shock and post-shock hematocrit levels to confirm that 50% hemodilution was achieved (Abbott Point of Care, Princeton, NJ) [17, 18].

Thrombelastography

Thrombelastography (TEG) was performed with blood collected from cardiac puncture at preshockand at the end of the experiment. One mL blood was anticoagulated with 100 μL 3.2% sodium citrate and vortexed briefly to avoid platelet clumping [19]. The citrated whole blood was allowed to sit for 30 min according to the manufacturer's instructions. Kaolin was used as an activator, and 340 μL of the blood was added to 20 μL of 0.2 M calcium chloride in a disposable plastic cup, with the assay performed on a TEG 5000 thrombelastograph hemostasis analyzer (Haemonetics, Niles, IL) at 37°C within 2 h of blood collection.

All TEG parameters were recorded from standard tracings: reaction time (R, min), coagulation time (K, min), angle (α, degrees), maximum amplitude (MA, mm), clot strength (G, dynes/cm^2), and estimated percentage lysis (LY30, Lysis at 30 min, %). The various components of the TEG tracing are depicted in Figure. 1 [12]. The SP is a measure of the time to initial clot formation, interpreted from the earliest resistance detected by the TEG analyzer causing the tracing to split; this is the terminus of all other platelet-poor plasma clotting assays (e.g., PT and aPTT). The R value, the time elapsed from start of the test until the developing clot provides enough resistance to produce a 2 mm amplitude reading on the TEG tracing, represents the initiation phase of enzymatic clotting factors. K measures the time from clotting factor initiation (R) until clot formation reaches amplitude of 20 mm. The angle (α) is formed by the slope of a tangent line traced from the R to the K time measured in degrees. K time and angle (α) denote the rate at which the clot strengthens and is most representative of thrombin cleavage of the fibrinogen into fibrin. The MA indicates the point at which clot strength reaches its maximum amplitude in mm on the TEG tracing, and reflects the end result of platelet-fibrin interaction *via* the GPIIb-IIIa receptors. G is a calculated measure of total clot strength derived from amplitude (A, mm) G ¼ (5000 3 A)/(100 3 A). The process of fibrinolysis leads to clot dissolution, leading to a decrease in clot strength; estimated percent lysis (LY30) measures the degree of fibrinolysis 30 min after MA is reached.

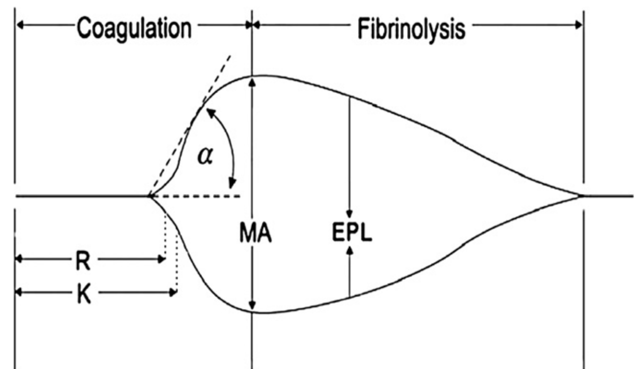

FIG. 1. TEG diagram. The following TEG parameters were recorded from standard tracings: reaction time (R, min), coagulation time (K, min), angle (α, degrees), maximum amplitude (MA, mm), clot strength (G, dynes/cm^2), and estimated percentage lysis (LY30, lysis at 30 min, %).

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