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Hypercoagulability in Porcine Hemorrhagic Shock is Present Early After Trauma and Resuscitation[1]

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Introduction. **The understanding of coagulopathy associated with trauma continues to evolve. Trauma patients are frequently coagulopathic early after injury and become hypercoagulable within days of injury. Thrombelastography (TEG) allows real-time evaluation of the coagulation status of patients. We hypothesized that TEG will identify post-traumatic hypercoagulable state in our porcine model of hemorrhagic shock and resuscitation.**

Methods. **Fourteen male Yorkshire pigs were sedated, instrumented, and splenectomized via laparotomy. Eight of these animals underwent a shock protocol consisting of a pulmonary contusion via captive bolt gun, 35% hemorrhage and two liver fractures. Vitals, hemodynamics, physiologic parameters and TEG were measured at baseline, after shock and at intervals after injury thru 72 h post-injury.**

Results. **Animals undergoing surgery and instrumentation demonstrated the same hypercoagulable patterns as animals that received shock, injury, and resuscitation. In this model, hypercoagulability was present in both groups at 4 h after injury and continued for 72 h post-injury (increased angle and maximum amplitude, $P < 0.05$, compared to baseline). Statistically significant differences between the groups were noted at both 16 and 48 h post-injury.**

Conclusions. **Hypercoagulability is present early after surgical intervention and trauma. This finding has implications for use of deep venous thrombosis (DVT) prophylaxis in trauma patients.**

Key Words: **trauma; hypercoagulable state; thromboelastography; deep venous thrombosis.**

INTRODUCTION

Hemorrhagic shock is a severe life-threatening emergency affecting all organ systems of the body [1]. A common consequence in severe injury is the development of coagulopathy [2]. Recent developments in trauma care have included early recognition and efforts to prevent and treat this problem. Our understanding of coagulopathy associated with trauma continues to evolve. The classic description of trauma-associated coagulopathy is a loss of coagulation factors due to bleeding, dilution from fluid administration, or massive transfusion and associated enzyme dysfunction of the coagulation proteases due to hypothermia and academia [3, 4]. Trauma patients are frequently coagulopathic early after injury and become hypercoagulable within hours to days of injury [3, 5].

Thromboelastography (TEG) allows real-time, rapid evaluation of the coagulation status of patients by documenting the interaction of platelets with the protein coagulation cascade to form initial platelet-fibrin interaction (r), through platelet aggregation (K), clot strengthening (α angle), and fibrin cross-linking (MA) to eventual clot lysis (LY30). TEG has been used for management of coagulopathic patients in the setting of combat injury in both Iraq and Afghanistan [6]. Interestingly, TEG has also been able to identify patients with post-injury hypercoagulability [7]. Shock and systemic hypoperfusion appear to be key components of the acute traumatic hypercoagulopathy that develops after initial therapy [3], with the hypercoagulability being defined as two or more of the following: short r and/or K time, increased α-angle, and increased MA [8].

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Patients after multisystem traumatic injury are at high risk for the development of a deep venous thrombosis (DVT) [5]. However, the proper timing of initiation of DVT prophylaxis continues to be an issue, especially in patients after head injury or with limited trauma-associated coagulopathy. Without the proper management of DVT, the rate of venous thrombosis and subsequent pulmonary embolism is substantial [9, 10]. We hypothesized that TEG will identify post-traumatic hypercoagulable state in our porcine model of hemorrhagic shock and resuscitation and may potentially serve as a tool for the early initiation for DVT prophylaxis in trauma patients.

METHODS

Animal Preparation

The University of Minnesota Institutional Animal Care Committee approved our study protocol. The care and handling of animals were in accord with the National Institutes of Health guidelines for ethical animal research.

A total of 14 male Yorkshire-Landrace pigs (Manthei Hog Farm, LLC, Elk River, MN) weighing 15 to 25 kg were fasted 24 h before surgery but were allowed water *ad libitum.* The pigs were anesthetized with an intramuscular dose of telazol 4-6 mg/kg (Fort Dodge Animal Health, Fort Dodge, IA). Anesthesia was maintained throughout the anesthetic portion of the experiment by intravenous infusion of propofol (AstraZeneca Pharmaceuticals, Wilmington, VA), along with 80% inhaled nitrous oxide. Pigs were orotracheally intubated and ventilated (Servo 900C; Siemens-Elema, Solna, Sweden). The FiO_2, inspiratory tidal volume and/or respiratory rate were adjusted to maintain a partial pressure of arterial oxygen (PaO_2) of 70 to 120 Torr and a partial pressure of arterial carbon dioxide ($PaCO_2$) of 35 to 45 Torr.

The right femoral artery was surgically exposed and a catheter placed so that the blood pressure could be measured continuously. Intermittent arterial blood samples were also drawn from this catheter. The right external jugular vein was surgically exposed and a 7 French introducer (Avanti, Cordis Corp., Miami Lakes, FL) and a Swan-Ganz catheter (5 French, Edwards Lifesciences, Irvine, CA) were placed to intermittently measure pulmonary artery occlusion pressure (PAOP), thermodilution cardiac output (CO), and mixed venous blood. A midline laparotomy and splenectomy were performed. Including the splenectomy in this portion of the study was to prevent autotransfusions and has been used as a model in other models of hemorrhagic shock [11, 12].

Catheters were placed into the urinary bladder (*via* a stab cystotomy) and into the inferior vena cava (IVC). An InSpectra StO2 system (Hutchinson Technology Inc., Hutchinson, MN) was placed on the left hind limb to monitor the perfusion status during the course of the experiment. The surgical preparation was followed by a stabilization period of at least 60 min or until the blood lactate levels *via* blood gas analyzer (Instrumentation Laboratory Co., Lexington, ME) were 2.0 mg/dL or less and the core temperature measured at least 37°C.

Polytrauma and Resuscitation Model

We induced polytrauma in animals ($n = 8$) by administering a pulmonary contusion *via* captive bolt gun, removing blood *via* the IVC catheter to obtain a systolic blood pressure (SBP) of <50 mmHg (typically, 35%–50% total blood volume over 21 min), and creating two liver fractures *via* a modified Holcomb clamp for a total shock time of 45 min. After 45 min of shock, and obtaining measurements, a limited resuscitation phase simulating transport to a trauma facility (1 h) began. During this period, lactated Ringers' (20 cc/kg/bolus) was administered if the systolic blood pressure was less than 80 mmHg. A standard resuscitation protocol was utilized to simulate common hospital resuscitation practice following the limited resuscitation phase (Fig. 1). Briefly, animals were resuscitated to standard clinical endpoints of systolic blood pressure (90 mmHg), urine output (1 cc/kg/h), and hemoglobin (≥6 g/dL) for 20 h. Twenty hours after initiation of full resuscitation, the animals were extubated and returned to postop for recovery. We followed the survivors for an additional 48 h. Surviving animals were euthanized and final samples obtained. An additional group of animals received anesthesia and instrumentation without tissue injury or hemorrhagic shock (negative controls, $n = 6$).

Physiologic parameters were monitored continuously throughout the experiment. These included heart rate (HR), mean arterial pressure (MAP), pulmonary artery pressure (PA), temperature, arterial oxygen saturation, BIS, and tissue oxygenation saturation (StO_2). Additional invasive hemodynamic parameters were measured at baseline (before hemorrhagic shock), during shock, at the end of shock, and then approximately every hour for 20 h after the initiation of resuscitation. These included cardiac output (CO), systemic oxygen delivery (DO_2), and systemic oxygen consumption (VO_2). Arterial and venous blood were analyzed *via* blood gas analyzer (Instrumentation Laboratory Co., Lexington, ME) for measurement of PaO_2, $PaCO_2$, mixed venous oxygen saturation (SvO_2), partial pressure of venous carbon dioxide ($PvCO_2$), blood hematocrit, base excess (BE)/base deficit (BD), and blood lactate levels. Thromboelastography (TEG) was measured on citrated blood samples at baseline and additional intervals throughout the experiment (Haemonetics Corp., Braintree, MA).

Organ function was assessed at eight time points throughout the course of the experiment by measuring bilirubin, albumin, total protein, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea nitrogen, creatine kinase (CK), creatinine, lactate dehydrogenase (LD), and platelet counts. A modified Glasgow Coma Score for veterinary use was obtained at four time points throughout the course of the experiment to assess the animals' cognitive status [13].

RESULTS

As expected, physiologic and hemodynamic data in animals that were shocked and resuscitated were

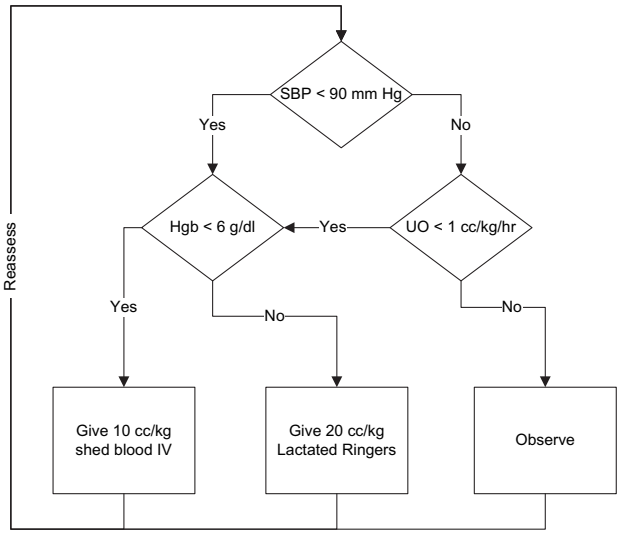

FIG. 1. A description of the resuscitation strategy utilized during the experiment procedure.