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A time course study of acute traumatic coagulopathy prior to resuscitation: From hypercoagulation to hypocoagulation caused by hypoperfusion?

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ABSTRACT

Introduction: Coagulopathy after sever injury predicts the requirements of blood products, organ failure and mortality in traumatic patients. The early onset and complexity of traumatic coagulopathy preclude the understanding the underlying mechanism. The aim of the study is to characterize the early coagulation alteration in a swine model with multi-trauma and shock.

Methods: Twelve pigs were subjected to multi-trauma (femur fracture, laparotomy, 10 cm intestine resection and grade III injury of liver) and hemorrhaged to a mean arterial pressure (MAP) of 40 mmHg. Physiologic parameters and coagulation variables (prothrombin time (PT), international normalized ratio (INR), fibrinogen, antithrombin-III (AT-III) activity, D-dimer and thromboelastography (TEG)) were measured after instrumentation (baseline), 5 min after multi-trauma (after trauma), 10 min (early shock) and 40 min (late shock) after hemorrhage. A group of 6 instrumented pigs were used as control.

Results: Multi-trauma and hemorrhage caused significant increase of base excess (BE) and lactate ($p < 0.05$). PT shortened after multi-trauma but increased significantly at late shock ($p < 0.05$). Fibrinogen reduced greatly after trauma and at early shock ($p < 0.05$), while remained stable afterwards. AT-III activity decreased throughout the experiment. Reaction time (R) shortened after trauma and at early shock (both $p < 0.05$). Maximal amplitude (MA) decreased significantly during the shock period.

Conclusion: After traumatic hemorrhagic shock, hypercoagulation turned into hypocoagulation in a short period, which was probably caused by hypoperfusion.

1. Introduction

Trauma is still a very common reason for mortality and morbidity in the 21st century [1,2]. Trauma induced hemorrhage accounts for around 40% of all trauma casualties [3]. Recently, acute traumatic coagulopathy (ATC) is recognized as a disorder of procoagulant, anticoagulant and fibrinolytic systems, which develops early after trauma and correlates with massive transfusion and mortality [4]. Tissue injury and systemic hypotension are considered to be the most important triggers of ATC [5]. Elevation of activated protein C (aPC), factor consumption, platelet dysfunction and fibrinolysis activation may all contribute to the coagulation changes. Brohi et al. have demonstrated the critical role of aPC at the early onset of the coagulopathy [6]. After binding to the thrombin–thrombomodulin (T–TM) complex, protein C (PC) is activated and could

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inhibit plasminogen activator inhibitor-1 (PAI-1) as well as factor VIII and V, thus activating fibrinolysis and suppressing coagulation.

Understanding the early changes of coagulation in trauma patients is crucial for the management of this traumatic coagulopathy especially under the situation without the results of laboratory test. Even though ATC develops quickly after shock and before massive fluid resuscitation, the mechanism responsible for the quick change remains speculative. Johansson and Ostrowski have proposed different coagulation responses to various trauma levels, in line with the concentration of plasma catecholamine [7]. Typically, patients with less trauma trend to have a normal or hypercoagulable state, whereas hypocoagulation or hyperfibrinolysis are more likely to be found in severely injured patients. Gando et al. have thought ATC was just another type of disseminated intravascular coagulation (DIC) (fibrinolytic phenotype), which had hyperfibrinolysis in the early stage and changed to antifibrinolytic phenotype within a few days of admission [8]. This theory is based on the fact that decreased fibrinogen and increased fibrin degradation products (FDP) are prevalent among ATC patients. Primary and secondary fibrinolysis are the results of massive thrombin generation, which leads to disseminated fibrin formation [9]. Therefore, consumptive coagulopathy and severe bleeding occur. According to this theory, which unifies ATC and classic DIC, hypocoagulation is the result of factor consumption and fibrinolysis due to pre-existed hypercoagulation. The question remains to be clarified is whether there is a hypercoagulable stage before the onset of hypocoagulation [10]. However, severely injured patients always show a tendency of bleeding and prolongation of clotting times, particularly in the early stage, even on-scene [11]. Whether the hypercoagulable period is missed remains unclear.

The purpose of this article was to characterize the changes of clotting function during the critical period after injury and prior to fluid resuscitation using TEG as well as conventional coagulation test in a swine model with complex trauma.

2. Materials and methods

This study was approved by the Institutional Animal Care and Use Committee of Nanjing University and followed national guidelines for the treatment of animals. Twenty-two domestic female pigs (weight 23.0 ± 2.5 kg) were used for the study. The experiment protocol was depicted in Fig. 1.

2.1. Anesthesia

The animals were fasted for 18 h before the surgical procedure, but allowed water ad libitum. Anesthesia was induced with ketamine (20 mg/kg) and atropine (0.06 mg/kg). With the animal positioned supine surgical preparation took place after skin preparation with povidone-iodine solution (10% wt/vol, Betadine Aqueous Antiseptic Solution, Seaton Healthcare Group plc, UK). Then, orotracheal intubation was performed, after which an esophageal thermometer was placed. Animals were allowed to breathe spontaneously for the remainder of the experiment unless they displayed marked respiratory depression, at which stage intermittent positive pressure ventilation was instituted in an attempt to maintain adequate oxygenation and prevent severe hypercapnea. Throughout the study anesthesia was maintained with intravenous injection of 150 $\mu g\ kg^{-1}\ min^{-1}$ propofol (Disoprivan 2%, emulsion; Astra Zeneca, Wedel, Germany) and bolus injection of 2–5 μg/kg fentanyl (Janssen Cilag, Neuss, Germany) to the clinical end points of reflexes and muscle relaxation as is done in humans.

2.2. Instrumentation and cardiovascular monitoring

The left carotid artery was cannulated to allow for continuous recording of MAP, and blood gas laboratory sampling. The right internal jugular vein was cannulated with a 5-Fr flow-directed thermodilution triple-lumen catheter (Arrow International Inc., Reading, PA) to allow for continuous monitoring of central venous hemoglobin oxygen saturation (ScvO2), blood gas sampling from the central venous circulation, and coagulation sampling. The left femoral artery was surgically exposed and cannulated to allow for rapid arterial hemorrhage. All of the ends of these catheters were tunneled subcutaneously, exteriorized between scapulae, and secured. A 12-Fr Foley catheter was inserted in the urinary bladder. After instrumentation, animals were allowed to equilibrate for a period of 15 min, and baseline measurements were obtained.

2.3. Grouping

The experimental group ($n = 16$) was subjected to multi-trauma and hemorrhage. A group ($n = 6$) instrumented as described above without multi-trauma and hemorrhage was used as control.

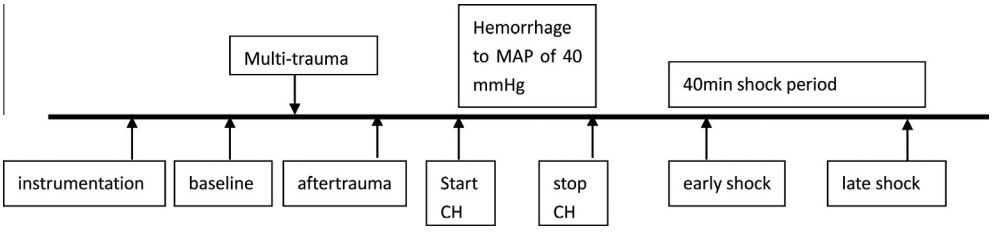

Fig. 1. Experimental protocol. CH, controlled hemorrhage.

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