ORIGINAL ARTICLES

Study of acute hemocoagulation changes in a porcine endotoxemic shock model using thrombelastography

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Disseminated intravascular coagulation and fibrinolysis have been associated with lipopolysaccharide (LPS)-induced endotoxemic sepsis. It has been well established by point-of-care (POC) thrombelastography (TEG) that pigs have a hemocoagulation pathophysiology that resembles humans. We evaluated the use of TEG during the development of coagulation abnormalities in a porcine model of endotoxemia. After approval by the Animal Welfare Committee, pigs were instrumented to record hemodynamic variables. Ten days after surgical instrumentation, LPS (50 μg/kg) was infused intravenously over a period of 45 minutes in conscious animals. Hemodynamic parameters were recorded before and for 6 hours after LPS infusion was completed. Simultaneously, blood samples were analyzed using TEG to measure reaction time (*R*), clotting time (*K*), alpha angle (α), maximum amplitude (MA), coagulation index (CI), percent lysis at 30 minutes, and percent lysis at 60 minutes. LPS induced profound hemodynamic changes associated with the induced endotoxemia. Concomitantly, a progressive consumption coagulopathy characterized by significant increases in *R* and *K* and decreases in α, MA, and CI developed. The overall hemocoagulation profile of the 3 nonsurviving animals (27%) was significantly different than that of the survivors. Fibrinolysis was not detected during the 6-hour evaluation period. All stages of clot formation were affected as demonstrated by TEG (increased *R* and *K*, decreased α and MA). Our results suggest that TEG is a rapid method for assessing coagulation abnormalities in early stages of endotoxemia in pigs. TEG could have significant clinical applications as a rapid POC method in human patients with sepsis. (Translational Research 2015;165:549–557)

Abbreviations: CI = coagulation index; CO = cardiac output; DIC = disseminated intravascular coagulation; dP/dt = ventricular contractility assessment; HR = heart rate; K = clotting time; kg = kilogram; LPS = lipopolysaccharide; LY = lysis; MA = maximun amplitude; mg = milligram; mm = millimeter; NIH = National Institute of Health; PA = plasminogen activator; POC = point-of-care; PT = prothrombin time; PTT = thromboplastin time; R = reaction time; SVR = systemic vascular resistnace; TAT = thrombin-antithrombin; TEG = thrombelastography; TEM = thrombelastometry; α = alpha angle

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AT A GLANCE COMMENTARY

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Background

The authors of this study evaluate the use of thrombelastography (TEG) as a point-of-care (POC) method to rapidly identify coagulation changes in severe sepsis. The experiment was performed in a large animal model of endotoxemia that resembles humans. The intention was to assess the potential value of the TEG tool in the clinical setting. We found that TEG was a rapid method to assess coagulation abnormalities in early stages of endotoxemia.

Translational Significance

This is a tool with potential applicability as a POC test (a bedside procedure) to assess the coagulation profile of septic patients. TEG could facilitate the early detection of individuals with more severe disease and consumption coagulopathy; consequently, it could lead to earlier and more aggressive treatment as well as provide prognostic clues in severe sepsis.

INTRODUCTION

Hemocoagulation abnormalities, including disseminated intravascular coagulation (DIC) and fibrinolysis, have been associated with sepsis.[1] DIC is more frequent in patients with shock,[2] which increases their risk of multiple organ failure and mortality.[3] Coagulopathies differ in their mechanism of activation. The most important pathway in sepsis appears to be the *extrinsic* route or tissue factor-dependent pathway.[4] Blocking the *intrinsic* pathway by administering factor XII–neutralizing monoclonal antibodies does not control DIC,[5] whereas administering factor VIIa–neutralizing monoclonal antibodies does.[6,7] Alterations to the hemocoagulation process, including lipopolysaccharide (LPS)-induced changes that occur in humans,[8,9] occur in pigs as well.[10-12]

The hematologic changes induced by sepsis are so complex that physicians are challenged to interpret them in clinical practice. Simpler techniques to assess coagulation abnormalities at the bedside are needed (point-of-care [POC]). Thrombelastography (TEG) is currently being used to manage coagulation abnormalities in obstetric patients[13,14] and to monitor trauma patients, patients undergoing cardiac surgery, and patients undergoing liver transplantation.[15-20]

Recently, TEG has also been used to characterize endotoxin-induced coagulopathy in vitro or in animal models.[21-23] Similar studies with humans[24] and pigs[25,26] have often used thrombelastometry (TEM), which also demonstrate several similarities between human and porcine coagulation,[27] but there have not been previous reports of TEG used in a porcine model of endotoxin-induced sepsis in conscious animals.

As a step toward understanding the development of coagulation abnormalities in humans, we assessed coagulation abnormalities associated with the hemodynamic changes encountered in a porcine model of endotoxemia using TEG, assessing whole-blood coagulation through the viscoelastic changes that occur during the clotting and lysis process. We hypothesized that TEG would detect coagulation changes associated with endotoxin-induced sepsis in pigs, as previously described by TEM, and in human sepsis.

MATERIALS AND METHODS

All procedures were approved by the University of Texas Animal Welfare Committee and were consistent with the National Institutes of Health "Guide for the Care and Use of Laboratory Animals" (NIH publication 85-23, revised 1985). This observational study was designed to assess hemocoagulation abnormalities by POC TEG with LPS-induced endotoxemia in conscious pigs.

Cardiovascular instrumentation. In preparation for the experiments, 11 adult female Yucatan mini pigs weighing 25–30 kg (Lone Star laboratory Swine, Seguin, Texas) were surgically instrumented. This experimental technique has been previously described in detail.[28,29] Briefly, animals were anesthetized with tiletamine (2–4 mg/kg intramuscularly) and isoflurane (2%), then intubated and prepared for sterile surgery. Animals were ventilated with a Harvard ventilator (Harvard Apparatus, South Natick, Massachusetts). An infusion of bretylium (5 mg/kg) was administered to prevent arrhythmia. Under aseptic conditions, a Tygon catheter was inserted into the descending aorta via the iliac artery. A left thoracotomy between the fourth and fifth intercostal space was performed, and the pericardium was incised. A miniature pressure transducer (6.5–7.0 mm; Konigsberg Instruments, Pasadena, California) was inserted into the left ventricle through an apical stab wound. A precalibrated flow probe (14–16 mm; Transonic Systems, Ithaca, New York) was positioned around the pulmonary artery. A second Tygon catheter was inserted into the left atrium, and a third Tygon catheter was inserted into the jugular vein for drug administration during the experimental protocol. All transducer leads and catheters were