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Development of a lethal, closed-abdomen, arterial hemorrhage model in noncoagulopathic swine

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ABSTRACT

Background: Prehospital treatment for noncompressible abdominal bleeding, particularly due to large vascular injury, represents a significant unmet medical need on the battlefield and in civilian trauma. To date, few large animal models are available to assess new therapeutic interventions and hemostatic agents for prehospital hemorrhage control.

Methods: We developed a novel, lethal, closed-abdomen injury model in noncoagulopathic swine by strategic placement of a cutting wire around the external iliac artery. The wire was externalized, such that percutaneous distraction would result in vessel transection leading to severe uncontrolled abdominal hemorrhage. Resuscitation boluses were administered at 5 and 12 min.

Results: We demonstrated 86% mortality (12/14 animals) at 60 min, with a median survival time of 32 min. The injury resulted in rapid and massive hypotension and exsanguinating blood loss. The noncoagulopathic animal model incorporated clinically significant resuscitation and ventilation protocols based on best evidenced-based prehospital practices.

Conclusion: A new injury model is presented that enables screening of prehospital interventions designed to control noncompressible arterial hemorrhage.

1. Introduction

Uncontrolled traumatic hemorrhage continues to be a dominant cause of death, accounting for almost 50% of potentially survivable battlefield casualties [1,2]. There are currently no available prehospital treatments for noncompressible intra-abdominal hemorrhage other than rapid transport to surgical care. Based on the critical nature of this problem, reproducible, lethal, large animal models are required to investigate new therapeutic protocols, pharmaceutical, and device interventions for hemorrhage control.

On the battlefield, the majority of arterial injuries occur due to explosions and gunshot wounds [3], whereas in civilian trauma, injury mechanism is split between blunt and penetrating trauma [4]. In an epidemiologic study of vascular injury in the Wars in Iraq and Afghanistan, White *et al.* [3] reported that the majority of vascular injuries within the torso involved the iliac artery (31%). In a survey of the National Trauma Data Bank, Markov *et al.* [4] observed that approximately 10% of noncompressible abdominal injuries were associated with the iliac artery. In military, patients who died of noncompressible torso hemorrhage, major arterial injuries were the

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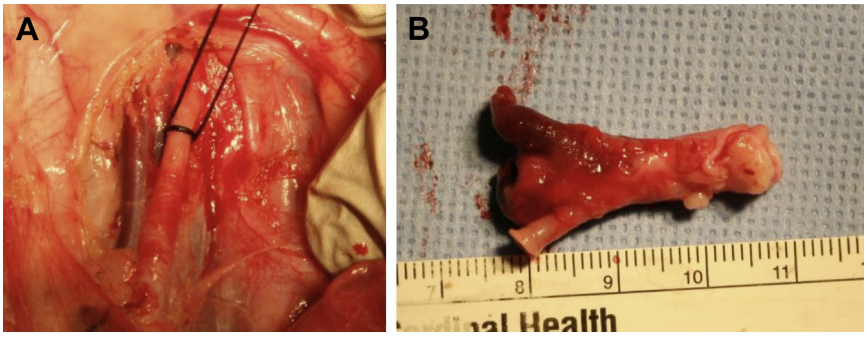

Fig. 1 – External iliac artery injury. The external iliac artery was dissected from retroperitoneal tissue and instrumented with a cutting wire (A). After the study, the relevant vasculature was explanted for analysis (B). (Color version of figure is available online.)

second-leading cause of mortality (26%; odds ratio with mortality 3.38) [5]. In a matched study of military and civilian noncompressible abdominal arterial injury, Markov *et al.* [4] demonstrated that the military population had a significantly lower mortality rate than civilian counterparts (11% *versus* 36%). In both civilian and military populations, noncompressible trauma represents a significant unmet need; novel therapeutic strategies must first be tested in preclinical animal models.

Several previous studies have used arterial injury models to investigate hemostatic agents for hemorrhage control. These studies have focused on variations of only two models: punch biopsy injuries in the open abdomen [6–8] and longitudinal dissection injuries in the closed abdomen [9–13]. These models vary in mortality and relevance to the prehospital setting.

We previously described a closed-abdomen, lethal, grade V hepatoportal injury model in noncoagulopathic swine [14]. Wires were placed strategically around hepatic vasculature and externalized percutaneously. Distraction of these wires resulted in severe uncontrolled hemorrhage and rapid mortality in a low-pressure, high-flow scenario. In this work, we hypothesized that a similar technique targeting arterial vasculature and simulating high-pressure, high-flow noncompressible injuries would result in severe uncontrolled hemorrhage and rapid mortality.

2. Materials and methods

2.1. Animals

Yorkshire swine (*Sus scrofa domestica*) 39–50 kg were obtained (Tufts University School of Veterinary Medicine, North Grafton, MA) and maintained in a facility accredited by the Associated for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC). The study was approved by the Institutional Animal Care and Use Committee of the Massachusetts General Hospital (IACUC) and the Animal Use and Review Office of the US Army medical Research and Materiel Command (ACURO). Animal received care in accordance with the Guide of the Care and Use of Laboratory Animals (Health, 2011 #17).

2.2. Instrumentation and monitoring

All swine ($n = 14$) were allowed to acclimate for 2 d and examined by a veterinarian to ensure good health. Food was withheld the night before surgery but access to drinking water was provided. On the day of surgery, animals were anesthetized with an intramuscular injection of 5 mg/kg Telazol (50 mg/mL of tiletamine hydrochloride and 50 mg/mL of zolazepam hydrochloride; Fort Dodge Animal Health, Overland Park, KS) mixed with 1.5 mg of atropine sulfate (Med-Pharmex Inc, Pomona, CA).

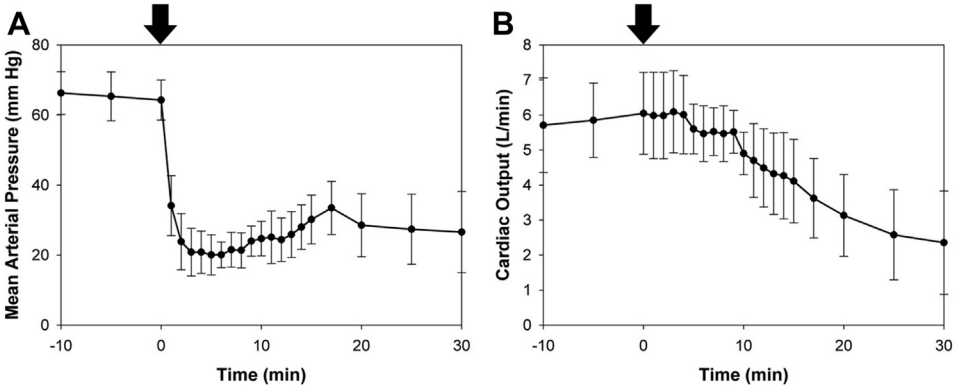

Fig. 2 – MAP (A) and CO (B) as a function of time. Vital signs dropped rapidly after injury at time = 0 (black arrows).