Background:
Hemorrhage and its complications are the leading cause of preventable death in combat casualties. Survival of hemorrhage is dependent on prompt hemorrhage control, sufficient - but not excessive - restoration of volume, and mitigation of ischemia/reperfusion injury by careful reintroduction of oxygen carrying capacity.

PEGylated carboxyhemoglobin bovine (PEG-HbCO) is a biological therapeutic that acts both as a carbon monoxide-releasing molecule (CO-RM) and as an oxygen transfer agent. It has been engineered to provide a low-level therapeutic release of carbon monoxide to inhibit vasoconstriction and attenuate immunological responses and then acts to transport oxygen preferentially to hypoxic cells and tissues.

Methods:
This study investigated the systemic (heart rate, mean arterial pressure) and microcirculatory (vasoactivity, interstitial fluid oxygenation \(P_{\text{O2}}\)) impact of two resuscitation fluids: a novel carbon monoxide/oxygen delivery agent (PEG-COHb Prolong Pharmaceuticals, LLC, South Plainfield, NJ), and a non-oxygen carrying colloid volume control (hetastarch; Hextend™, William H. Nugent™, South Plainfield, NJ), and a non-oxygen carrying colloid volume control (hetastarch; Hextend™, William H. Nugent™, South Plainfield, NJ). Male Sprague-Dawley rats underwent a transplantation and were maintained in this hypovolemic, hemorrhagic shock phase for 30 minutes. Resuscitation fluids were infused at a rate of 3.5 ml x min\(^{-1}\) x kg\(^{-1}\) through a cannulated carotid artery and were maintained in this hypovolemic, hemorrhagic shock phase for 30 minutes. Resuscitation fluids were infused at a rate of 3.5 ml x min\(^{-1}\) x kg\(^{-1}\) to a volume equal to 20% of the total estimated blood volume through a cannulated jugular vein. Systemic measurements were recorded via a cannulated femoral artery that was connected to a pressure transducer (MP150; Biopac Systems, Inc, Goleta, CA) while microcirculatory parameters were collected through phosophorescence quenching and intravital microscopic examination of the exteriorized spinotrapezius muscle. Blood was collected in PAXgene RNA tubes at baseline and at the end of experiment to quantify white blood cells mRNA levels.

Summary:
In a hemorrhagic shock model PEG-COHb was shown to have superior resuscitative properties as compared to Hextend™. PEG-COHb extended survival time > 8 hours, nearly twice as long as animals resuscitated with Hextend™. Furthermore, PEG-COHb was shown to deliver oxygen to hypoxic tissues without inducing adverse vasoactivity. RNA PCR analysis showed that PEG-COHb could prevent or reverse the upregulation in pro-inflammatory RNA associated with traumatic blood loss. The combination of PEG-COHb ability to transport and deliver oxygen to hypoxic tissues with CO release to attenuate inflammatory response, supports the clinical use of PEG-COHb in not only trauma, but also other indications which result in hypoxia. Currently PEG-COHb is in phase 2 clinical trials for sickle cell anemia, delayed graft function, delayed cerebral ischemia, and in indications where blood transfusion is not an option.