

LOW-VOLUME RESUSCITATION FROM TRAUMATIC HEMORRHAGIC SHOCK WITH Na⁺/H⁺ EXCHANGER INHIBITOR

*Wu, Dongmei; *Dai, Hui; *Arias Jacqueline; **Latta, LL

*Pearlman Biomedical Research Institute, Mount Sinai Medical Center, Miami Beach, FL;

**University of Miami, Miami & Coral Gables Campuses, FL

INTRODUCTION:

Severe hemorrhage from traumatic injury is a major causative factor in almost half of the deaths on the battlefield, especially during the early period (<2h) after injury.¹ Intervention with low-volume fluid resuscitation is increasingly preferred to more aggressive fluid replacement.^{2,3} Na⁺/H⁺ exchanger (NHE) inhibitors have not been studied in a hemorrhagic shock model elsewhere. Our preliminary study has shown that NHE1 inhibition delayed the onset of hypovolemic circulatory shock in a graded hypovolemia model in pigs, improved resuscitation outcomes and survival in prolonged hypovolemic circulatory shock. The goal of this proposal is to investigate the effects of NHE inhibition by BIIB513, a novel pharmacological agent in enhancing the overall outcomes of hemorrhage and trauma, and to understand related mechanisms. The specific aim is to show that NHE inhibition prevents early death caused by cardiac arrest, and prevents multiple organ failure by inhibiting neutrophil infiltration and NF- κ B activation, thereby, reducing systemic inflammation, and thus multiple organ injuries in a rat model of hemorrhagic shock.

METHODS:

28 Sprague Dawley male rats weighing 300-360 g were anesthetized and a closed, mid shaft femur fracture induced via a three-point bending to a fixed displacement creating a consistent degree of soft tissue injury.⁴ They then remained under anesthesia with infusion of ketamine and Xylazine. The animals were then bled via the carotid artery to maintain a mean arterial pressure of 40 mmHg for 20 minutes. Groups: 1) no therapy; 2) 15 ml/kg Hextend infusion over 40 minutes; 3) 3 mg/kg BIIB513 (NHE-1 inhibitor) + 15 ml/kg Hextend infusion over 40 minutes. Blood oxygen content was monitored throughout the observation period. After 4 hours, the animals who survived received a second infusion of Hextend. The experiment was terminated at 6 hours after initial resuscitation.

Tissue samples from the brain, heart, liver, and lung were prepared for histological analysis. Enzyme immunoassay kits for tumor necrosis factor-alpha (TNF- α) (R & D Systems), soluble

intercellular adhesion molecule1 (sICAM-1) (R & D Systems), and for C-reactive protein (CRP) (Life Diagnostics, Inc., West Chester, PA) were used to determine the concentrations of these mediators in the plasma. Neutrophil accumulation in the liver was measured by determining myeloperoxidase (MPO) activity according to previously published methods.^{1,3} MPO activity in each sample was determined by measuring the change in absorbance at 460nm. Each sample was tested in triplicate. One unit of MPO activity is the amount of enzyme that will reduce 1 μ M peroxide per minute. MPO activity was expressed as units per 100 milligram weight of tissue.

All data was reported as mean \pm SD. Statistical differences were determined by analysis of variance for repeated measures followed by Student's modified *t*-test with Bonferroni correction for multiple comparisons. P values <0.05 were considered to indicate significant differences.

RESULTS:

All animals in the no therapy group died within 2 hours. Compared to Hextend infusion alone, the addition of NHE-1 inhibition with BIIB513, improved the hemodynamic response to fluid resuscitation (Fig 1), increased blood oxygen content, prevented metabolic acidosis, and improved 6 hour survival (42% in Hextend group vs 80% in BIIB513 + Hextend group). (Fig. 2) NHE-1 inhibition also resulted in reduced plasma levels of TNF- α , ICAM-1 and C-reactive protein, and attenuated neutrophil infiltration in the liver. There were no morphologic changes found in any of the tissue samples at this early time period.

DISCUSSION:

NHE-1 inhibition with BIIB513 improved the hemodynamic response to fluid resuscitation, attenuated tissue inflammatory mediators, and most importantly improved survival. These results provide information to fill the gaps of our current knowledge, expand our understanding of the mechanism of hemorrhagic shock in humans and provides two potential new life saving therapeutic modalities.

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Mean Arterial Pressure

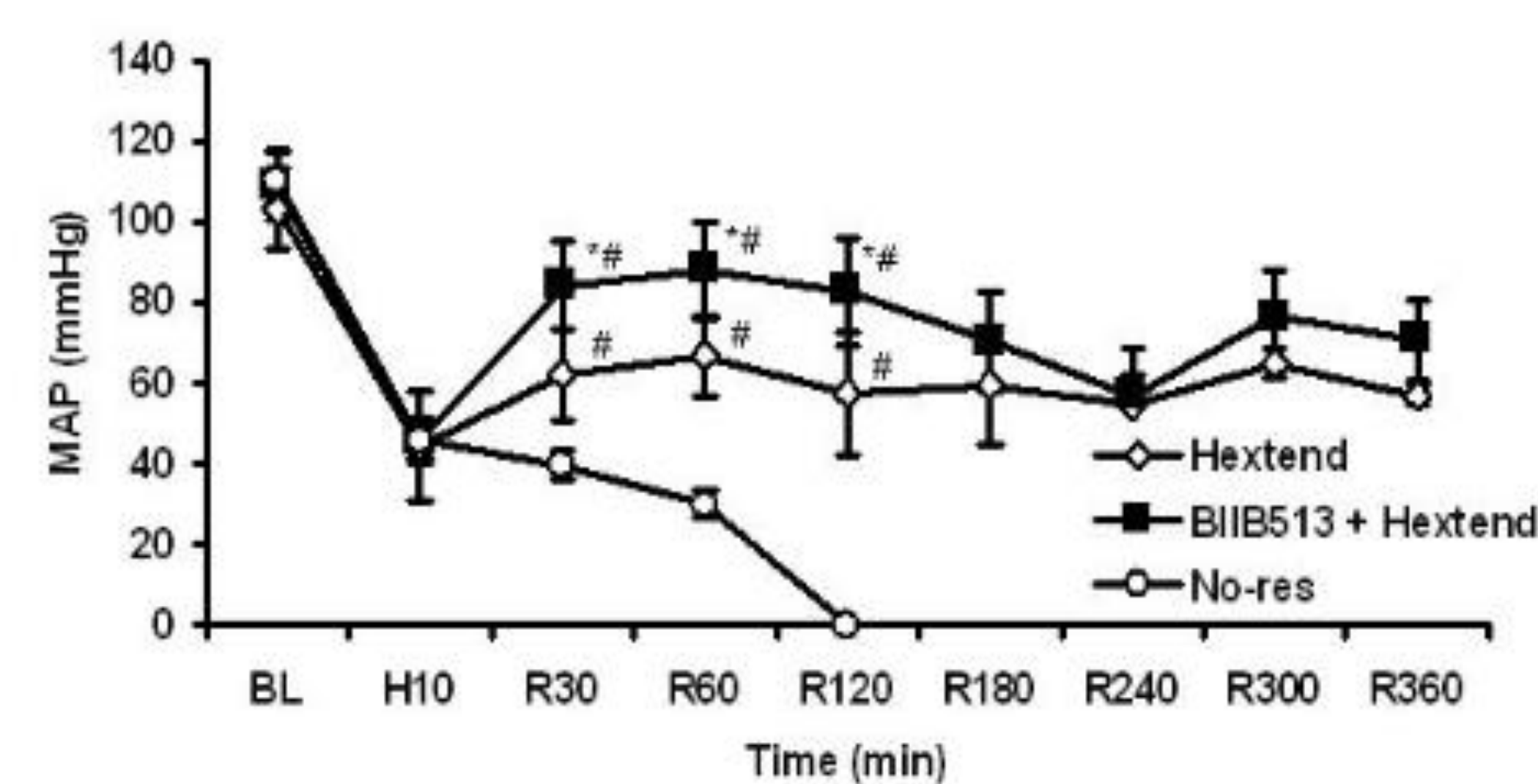


Figure 1 - Mean Arterial Pressure vs. Time

Survival after hemorrhagic shock

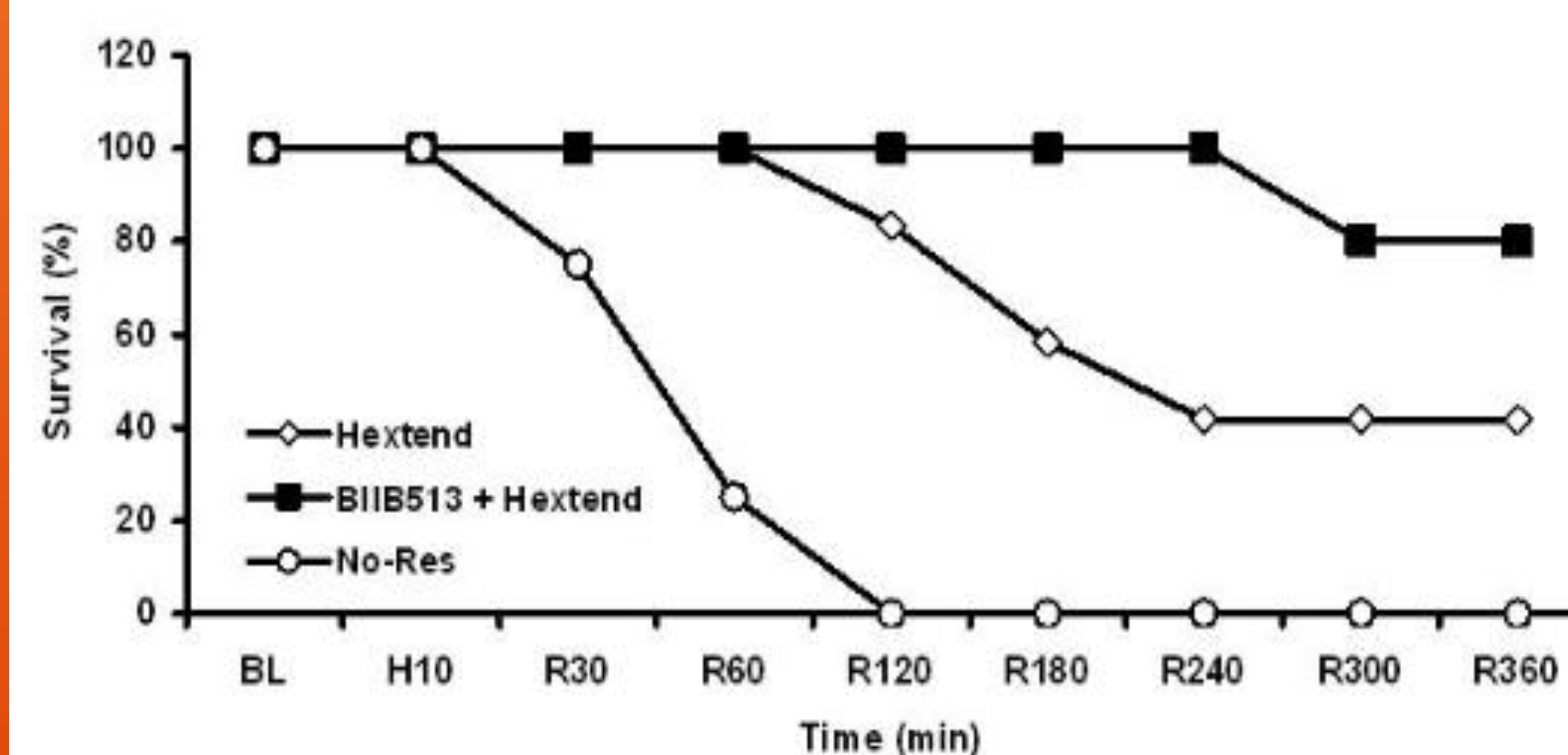


Figure 2 - Results - % Survival vs. Time