

## EFFECT OF RESUSCITATION USING PLASMA-DERIVED EXOSOMES IN A MURINE HEMORRHAGIC SHOCK MODEL

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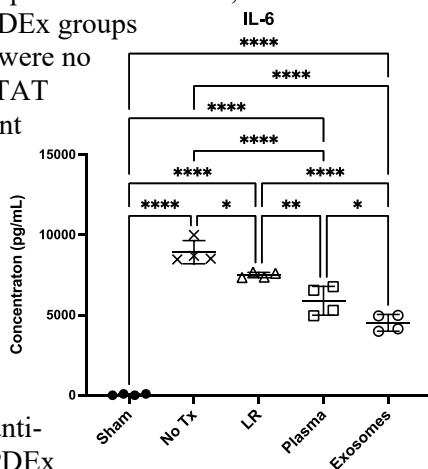
**Introduction:** Hemorrhagic shock remains the second-leading cause of early trauma-related mortality. Transfusion of plasma products has been shown to increase survival. Exosomes, which are released by all cell types, are a type of extracellular vesicles currently being investigated as potential treatment options in other pathologies. In this study, we aim to investigate the effect of resuscitation using plasma-derived exosomes (PDEx) in a murine hemorrhagic shock model.

**Methods:** C57BL/6 (WT) mice were subjected to a fixed-pressure hemorrhagic shock model in which 50% of the total blood volume is withdrawn to achieve a mean arterial pressure of 25mmHg for a 3-hour duration. At 90 minutes, resuscitation using 200 $\mu$ L of LR, murine plasma, or  $1 \times 10^{10}$  murine PDEx was administered. At 180 minutes, blood was collected, and TNF- $\alpha$ , IL-6, Syndecan 1 (Sdc 1), and thrombin-antithrombin complex (TAT) concentrations in plasma were measured using ELISA-based kits.

**Results:** In comparison to the sham group, TNF- $\alpha$ , IL-6 levels, and Sdc 1 levels increased in all treatment groups following hemorrhagic shock, with the highest concentrations being in the no treatment (Tx) group, followed by the lactated Ringer's (LR) treatment group. Alternatively, shock decreased TAT concentrations in the no Tx and LR groups to similar levels, with no significant level changes in the plasma and PDEx groups when compared to sham.

Furthermore, there were no significant differences in TNF- $\alpha$ , Sdc 1, and TAT levels between the plasma and PDEx treatment groups. However, mice who received PDEx showed lower post-shock IL-6 values in comparison to mice who received plasma (4519 vs 5895 pg/mL,  $p < 0.0247$ ).

**Conclusion:** In mice, resuscitation using PDEx demonstrated comparable effects to plasma resuscitation. Furthermore, PDEx treatment showed lower IL-6 levels than those of plasma treatment, implying greater anti-inflammatory effects. Our data suggest that PDEx may be a future therapeutic option for traumatic hemorrhagic shock.



## IL-1RA AND IL-10 IN ABDOMINAL REACTIVE ASCITES MAY REDUCE MESOTHELIAL ADHESION-LIKE FIBER FORMATION

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**Introduction:** Postoperative adhesions and subsequent bowel obstruction may occur following abdominal surgery. Appendectomy (appy) is an independent risk factor for adhesion-related rehospitalization. Disrupted during surgery, mesothelial cells (MCs) on the surface of the peritoneum secrete a sugar-rich glycocalyx to ensure a non-adhesive surface. Trauma and inflammation activate MCs to form adhesions, and pathologic adhesions may arise if adhesion fibrinolysis and MC secretion of glycocalyx is disrupted. Proteins disrupting these processes may originate from peritoneal reactive ascites (rA). Here, we analyze inflammatory mediators associated with distinct phenotypes of human MCs treated with rA collected during appy or adhesiolysis for small bowel obstruction (SBO).

**Methods:** This is a prospective observational IRB-approved study at three Level 1 trauma centers where peritoneal rA is collected prior to surgical intervention for non-perforated appendicitis or SBO. 71 cytokines/chemokines and 14 soluble receptors (HD48, HD23, HDSCR14; EVE Technologies) were quantified in rA. MCs were exposed to 48h of rA stimulation. Cell phenotypes were scored for 47 appy and 12 SBO rA by light, for adhesion-like fibers, and fluorescence microscopy, for glycocalyx, with labeled sugar-binding lectins: Concanavalin A and Wheat Germ Agglutinin. Scores over 3 independent experiments were clustered into 4 “fiber-lectin” (F-L) groups: No F-low L (NF-LL), No F-high-L (NF-HL), high-F-HL (HF-HL), and HF-LL. Prior abdominal surgeries (PAS) was dichotomized into No-PAS/PAS. Analyses were performed in Metaboanalyst 5.0.

**Results:** With 76 analytes detected in rA, 2-way ANOVA analysis of F-L and PAS showed significant differences in 19 and 10 analytes. Three analytes in common showed higher concentrations in NF-NL/No-PAS rA (adjusted  $P < 0.001$ ) and were Interleukin (IL)-1 receptor antagonist (RA), Eotaxin-2, and IL-10. NF-NL-associated rA showed a higher concentration of IL-8 compared to the other phenotypes (adjusted  $P < 0.001$ ).

**Conclusions:** Glycocalyx was associated with decreased proinflammatory IL-8. IL-1RA and IL-10 are anti-inflammatory and may reduce adhesion-like fiber formation in PAS rA-treated MCs, while increasing glycocalyx.

## REAL TIME DETECTION OF GLYCOCALYX DEGRADATION FOLLOWING TRAUMA: A CONCEPTUAL USE OF THROMBOELASTOGRAPHY

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**Introduction:** Endothelial injury and glycocalyx shedding occur early after trauma/hemorrhagic shock (T/HS). It has been demonstrated that endothelial glycocalyx (EG) degradation is associated with increased vascular permeability and barrier dysfunction. It remains controversial as to whether EG components contribute to traumatic coagulopathy and resultant bleeding complications. Viscoelastic tests (VETs) such as thromboelastography (TEG) have been used to characterize hemostasis and coagulation following T/HS. Current VETs use activators to provide quicker results in patients following T/HS and other shock states. We hypothesize that use of these activators such as kaolin and tissue factor may affect TEG coagulation parameters vs. when no activators are used (Native TEG). This may minimize the resultant effect of glycocalyx components such as heparan sulfate (HS) or syndecan-1 (syn-1) on TEG results. This was studied using an *in vitro* model.

**Methods:** Citrated whole blood (WB) samples were recalcified and spiked with HS and syn-1 at clinically relevant concentrations. Blood samples were subsequently processed using a TEG-5000 or 6s analyzers. Parameters studied included citrated kaolin (CK) R time, R time with heparinase to detect a “heparin” effect (CKHR) and native TEG R time (no activators). Other parameters studied included angle and maximum amplitude (MA); clot dynamics and strength, respectively.

**Results:** Mean  $\pm$  SD (N = 5 for each group)

\*p<0.05 vs. Whole blood,  
#p<0.05 vs. Whole blood +  
HS (35 $\mu$ g/ml).

There was no effect on TEG parameters by syn-1, except for an increase in CK R time at the 200 ng/ml concentration.

**Conclusion:** The anticoagulant effect of EG

degradation products were associated with HS in this study. The results of our study suggest that the use of activators (Kaolin or tissue factor) may mask the effects of endothelial glycocalyx (EG) degradation products on TEG coagulation parameters. This was evident with native TEG or when comparing TEG R time  $\pm$  heparinase. The latter comparison may be a novel real time and readily available test to identify “hidden” coagulation effects of EG degradation products.

	Whole blood	Whole blood + HS (35 $\mu$ g/ml)	Whole blood + HS (100 $\mu$ g/ml)
CK R time	6.0 $\pm$ 0.7	7.9 $\pm$ 0.3*	11.6 $\pm$ 0.5*#
CKH R time	6.4 $\pm$ 0.3 ( $\Delta$ 0.4)	5.4 $\pm$ 0.5* ( $\Delta$ 2.5)	5.5 $\pm$ 0.3* ( $\Delta$ 6.1)
Native TEG R time	9.0 $\pm$ 0.5	15.8* $\pm$ 1.1	20.5 $\pm$ 1.3*#
MA	57.2 $\pm$ 3.3	53.9 $\pm$ 4.5	49.3 $\pm$ 2.8*
Angle	70.1 $\pm$ 6.2	65.6 $\pm$ 4.2	55.5 $\pm$ 4.1*#

\*p<0.05 vs. Whole blood, #p<0.05 vs. Whole blood + HS (35 $\mu$ g/ml).

## A COMPARISON OF WHOLE BLOOD WITH TRANEXAMIC ACID TO OTHER RESUSCITATIVE MEASURES IN TRAUMA PATIENTS

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**Introduction:** Current resuscitative strategies for traumatic hemorrhagic shock include tranexamic acid (TXA) administration and use of whole blood (WB) or packed red blood cells (PRBC). Given the different coagulation properties of WB and PRBC, we aimed to determine if TXA had a significant impact on outcomes in transfused trauma patients.

**Methods:** Our institutional trauma registry was queried for all injured patients who received any transfusion between 2015 and 2022 within 4 hours of arrival. Patients were divided into three groups: 1) WB+TXA, 2) WB alone, or 3) PRBC+TXA. Demographics, vital signs, injury severity score (ISS), trauma score and injury severity score (TRISS), comorbidities, incidence of massive transfusion (MT), disposition from the Trauma Resuscitation Unit (TRU), 6-hour, 24-hour, and 30-day mortality were compared. We also compared the rates of pulmonary embolism (PE), deep vein thrombosis, unplanned returns to OR, acute kidney injury, and pulmonary complications.

**Results:** A total of 582 patients met inclusion criteria. There were no differences in ISS or TRISS between the cohorts. When compared to the PRBC+TXA cohort, the WB+TXA and the WB only cohorts were less likely to require MT or need surgical intervention emergently from the TRU. There was no difference in mortality. A higher rate of pulmonary embolism (PE) was noted in the WB+TXA cohort (See Table 1).

**Conclusion:** While the type of blood product transfused with or without TXA

does not appear to affect mortality, trauma patients who

Table 1	TXA + WB (n=213)	WB only (n=302)	TXA + pRBC (n=67)	P-value
MT, n (%)	15 (7.0%)	16 (5.3%)	23 (34.3%)	<0.0001
OR, n (%)	87 (40.8%)	95 (31.5%)	41 (61.2%)	<0.0001
PE, n (%)	14 (6.6%)	8 (2.6%)	1 (1.5%)	0.0434

receive WB with or without TXA are less likely to require MT or surgical intervention compared to PRBC with TXA. Additionally, WB with TXA may be associated with a higher rate of PE. Additional studies are needed to better assess this potential risk.

## COMPARISON OF CLINICAL JUDGMENT VS THE BLEEDING RISK INDEX IN PREDICTING TRANSFUSION

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**Introduction:** Significant bleeding after trauma is the most frequent cause of preventable death. The Bleeding Risk Index (BRI) is a “big data” model that predicts the use of transfusion for adult trauma patients, based on automatically collected vital signs. We hypothesized that the BRI would predict blood transfusion with greater sensitivity and specificity compared to clinical judgment.

**Methods:** Within 10-15 minutes of arrival, a research team member requested paramedics, nurses (RN), and physicians (MD) to complete a survey using clinical judgment to predict a patient’s transfusion outcomes, including un-cross matched red blood cell (UnX), or any transfusion within 6 and 24 hours. BRI predictions were calculated during the same timeframe. The areas under the Receiver Operating Curves (AUCs) were calculated for comparison.

**Results:** A total of 574 trauma patients were prospectively enrolled from August 2021 to June 2022, with mean age of 42.5 years (SD 18.3) and 78% being male. 11.6%, 27.5%, and 30.5% patients received UnX, or any transfusion within 6 and 24 hrs respectively. BRI prediction had AUCs 0.84, 0.85, and 0.81 for UnX, and any transfusion within 6 and 24 hours. Paramedics had AUROCs of 0.66, 0.66, and 0.70. RN had AUROCs of 0.76, 0.79, and 0.76. MD had AUROCs of 0.77, 0.79, and 0.77 respectively. Delong’s AUC comparison showed that BRI predictions were significantly more sensitive and specific ( $p<0.05$ ) compared to human experts’ predictions, except that the algorithm performed similarly well ( $p=0.065$ ) to MDs in predicting 24-hour blood transfusion.

**Conclusions:** This study demonstrated that BRI, generated from a large-scale dataset, predicts the urgent use of blood better than human experts during trauma resuscitation, and may be able to enhance decision-making in austere trauma settings by less experienced providers.

## PARTIAL REBOA ENABLES CT IMAGING AND INCREASED USE OF ENDOVASCULAR HEMORRHAGE CONTROL

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**Introduction:** Historically, the use of REBOA was followed by immediate hemorrhage control, often accomplished through damage control techniques in the operating room. Numerous pre-clinical studies have demonstrated the benefits of partial REBOA, including early temporization of non-compressible truncal hemorrhage while mitigating distal ischemia. We hypothesize that the utilization of a REBOA device designed also to provide partial aortic occlusion (pREBOA) shifts Emergency Department (ED) disposition away from the operating room (OR) and towards computed tomography (CT) and endovascular interventions (EVIR) when compared to the previous ER-REBOA.

**Methods:** Data from the AAST AORTA Registry between 9/26/2013-1/10/2023 were used to compare the methods of hemorrhage control (OR vs EVIR) between patients treated with ER-REBOA and pREBOA. EVIR included any angiography procedure regardless of physical location, such as Interventional Radiology (IR), IR in the OR, or hybrid suite. OR interventions included other abdominopelvic hemorrhage control techniques, such as laparotomy or pre-peritoneal packing. Patients who did not survive to intervention were excluded.

**Results:** Both ER-REBOA and pREBOA groups were similar in initial demographics (Table 1); however, there was increased use of partial occlusion in the pREBOA group. pREBOA significantly altered the initial disposition of patients from the ED ( $p=0.03$ ). When evaluating reasons for aortic occlusion, there was a significant increase in the use for stabilization to CT and a decrease in stabilization for OR ( $p=0.008$ ). There was also a nearly doubled rate of endovascular-only procedures in the pREBOA group at 13.5% from 7.3% ( $p = 0.03$ ). (Table 2)

**Conclusion:** The use of pREBOA was associated with a significant decrease in ED disposition to OR, an increase utilization of CT scan, and an increased use of EVIR as a means of hemorrhage control. While further research is required, these results suggest the use of pREBOA may reshape how providers triage critically ill patients to the OR, EVIR, or CT.

**Table 1:** Demographics, clinical presentation and injury severity among patients with ER-REBOA vs. pREBOA

Variable	ER-REBOA (n=752)	pREBOA (n=110)	P-value
Age	42	33	0.002*
% Penetrating	78.5%	78.5%	0.99
ISS	34	34	0.84
Initial SBP	97	98	0.63
Initial HR	105	110	0.51
Initial GCS	8	6	0.32
Prior CPR	22.3%	21.8%	0.90

Variables shown as median (Q1, Q3) or percentage.  
 Injury Severity Scale (ISS), Systolic Blood Pressure (SBP), Heart Rate (HR), Glasgow Coma Scale (GCS), Cardio-Pulmonary Arrest (CPR)

**Table 2:** Outcomes between patients with ER-REBOA vs. pREBOA

Variable	ER-REBOA	pREBOA	P-value
% Zone 1 Occlusion	65.9% (740)	74.1% (108)	0.13
% Partial Occlusion	11.2% (170)	84.9% (106)	<0.0001*
<b>REBOA Reason</b>	n = 181	n = 96	0.008*
Stabilization for CT	18%	33%	
Stabilization for OR	46%	26%	
<b>ED Disposition</b>	n = 642	n = 96	0.03*
To OR	75.5%	67.7%	
To EVIR	7.3%	13.5%	

Outcome data between two groups based on available data; (n) specified for each analysis.  
 Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA), Emergency Department (ED), Operating Room (OR), Endovascular Interventional Radiology (EVIR).

## PREDICTING HIGH-INTENSITY RESUSCITATION NEEDS IN INJURED PATIENTS FOLLOWING HEMOSTASIS

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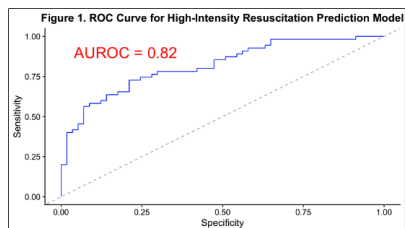
**Introduction:** Resuscitation needs following hemostasis are heterogeneous and influence outcomes and resource utilization. No predictive capability exists in the post-hemostasis phase of care to anticipate high-intensity resuscitation (HIR) needs. We sought to define HIR and hypothesized that HIR can be predicted from data available at the time of ICU admission.

**Methods:** Hemodynamic, laboratory, and procedure data for consecutive injured patients (2016-19) admitted to the trauma ICU following an emergent operation or angiographic intervention were reviewed. HIR thresholds were defined as: a) the top decile of blood products or crystalloid provided in the ICU ( $\geq 3$  units,  $\geq 4$  liters, respectively) during hours 0-12 after admission and/or b) persistent vasoactive medication use, between ICU hours 2-12. The primary outcome (HIR) was a composite of *any* of the above criteria. Logistic regression models for HIR with predictor variables selected by LASSO regression were created using 70% of the cohort. Performance of the models was determined by AUROC using the remaining 30%.

**Results:** Data from six-hundred-and-five (605) subjects were analyzed. The median age was 39 [IQR: 28-52], ISS was 26 [IQR: 17-38], 79% were male and 41% of the cohort suffered penetrating injuries. HIR prevalence is depicted in **Table 1**. LASSO selected predictor variables included ICU admission: shock index, lactate, base deficit, hematocrit, and INR. The predictive model achieved an AUC of 0.82 (**Figure 1**) using only commonly available hemodynamic and laboratory data from the time of ICU admission.

**Conclusions:** Post-hemostasis, ICU admission data can predict subsequent high-intensity resuscitation. Though prospective model validation is warranted, the ability to predict HIR will help in determining future resource utilization and staffing in critical care environments.

Table 1. High-Intensity Resuscitation Prevalence	
High-Intensity Resuscitation	36% (215/605)
Blood Products ( $\geq 3$ units)	11% (67/605)
Crystalloid ( $\geq 4$ liters)	15% (88/605)
Persistent Vasopressors (ICU 2-12h)	24% (143/605)



## ROLE OF IONISED CALCIUM IN TRAUMA RESUSCITATION- A PROSPECTIVE STUDY AT A LEVEL I TRAUMA CENTER

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**Introduction:** Trauma resuscitation aims at early restoration of homeostasis by reversing the metabolic derangements caused predominantly by bleeding. With evolving evidence on trauma-induced hypocalcaemia it remains empirical to consider these perturbations early during trauma resuscitation. Nevertheless, no proper guidelines exist regarding evaluation of these dysregulations and also its supplementation. Hence, we designed a prospective study to analyze the role of ionized calcium in trauma resuscitation in our setting. The objective of this study was to establish the prevalence of hypocalcaemia in trauma patients and to analyse its association with mortality and the need for blood transfusion.

**Methods:** A prospective study was conducted on trauma patients admitted to a Level 1 trauma center in India between September 2020 and June 2022 who met the inclusion and exclusion criteria. Ionised calcium was analysed using arterial/venous blood gas immediately on arrival, after 6hrs, and on day 2 of injury. The amount of blood transfusion received by the patient was noted along with other demographic and in-hospital details.

**Results:** Of the 1961 patients eligible for the study 200 patients were recruited and analysed. 72.5% of patients were hypocalcaemic on arrival. There was a significant association between ionised hypocalcaemia and mortality (p-value 0.0085). Ionised calcium was also significantly associated with the need for blood transfusion (p-value <0.01). However, ionised calcium was not a sensitive or specific predictor in itself to predict the need for blood transfusion. Both the univariate and multivariable analysis showed ionised hypocalcaemia to be an independent predictor of mortality.

**Conclusions:** Ionized hypocalcaemia is widely prevalent among acutely injured. Hypocalcaemia at admission is associated with increased mortality as well as an increased need for blood transfusions.



## THE FOG HAS NOT LIFTED: NO REDUCTION IN COMPLICATIONS FOR PARTIAL REBOA IN THE AAST AORTA REGISTRY

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**Introduction:** Resuscitative Endovascular Balloon Occlusion of the aorta (REBOA) is a potentially lifesaving, but polarizing therapy due to the associated morbidity and uncertainty of who might benefit. Techniques like partial (p)REBOA to provide hemodynamic support while reducing distal ischemia are now captured in the AAST Aortic Resuscitation in Trauma and Acute Care (AORTA) registry. We hypothesized that pREBOA would be associated with improved mortality and fewer adverse outcomes.

**Methods:** We queried the AAST AORTA registry for patient demographics, clinical characteristics, intervention characteristics, and outcomes between 2020-2022. Adult patients who received complete (c)REBOA or pREBOA were considered for inclusion. Patients were excluded if they had a head AIS  $\geq 3$  or an AIS of 6 in any body region.

**Results:** A total of 164 patients that met inclusion criteria were identified. Partial REBOA was used in 36% of cases. There was no significant difference in patient demographics, injury characteristics, or injury severity between pREBOA and cREBOA. There was no difference in mortality rate (44% vs 45%). After adjusting for potential confounders with Poisson regression analysis, no statistically significant difference in complications was detected between the two different REBOA approaches [adjusted IRR (95% CI): 1.11 (0.54-2.27),  $p = 0.777$ ]. This association persisted during subgroup analysis of aortic Zone 1 vs. Zone 3 deployment. Notably, metrics on duration of cREBOA or pREBOA were not collected in the AORTA registry and >40% of patient entries were missing time to definitive hemorrhage control data.

**Conclusion:** Based on this registry analysis, pREBOA did not reduce morbidity or mortality compared to cREBOA. Improving granularity of important clinical metrics in the AORTA registry is essential to understanding whether patients will benefit from pREBOA and how to best guide implementation of this controversial resuscitation adjunct.