RECOMBINANT ADAMTS13 MITIGATES LUNG DYSFUNCTION IN MICE AFTER POLYTRAUMA AND HEMORRHAGE SHOCK

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BACKGROUND: Severe trauma with hemorrhagic shock (HS) is associated with endothelial injury, resulting in release of hyperadhesive ultra-large von Willebrand Factor (VWF). Clinical studies further show that low levels of VWF-cleaving enzyme ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motifs member 13) are associated with worse outcomes after trauma. We *hypothesized* that exogenous ADAMTS13 could reduce VWF hyperadhesive activity and prevent organ dysfunction after acute trauma. We tested this hypothesis in our mouse model of polytrauma and HS.

METHODS: C57BL/6J mice underwent polytrauma (gastrocnemius muscle crush, tibial fracture, and laparotomy) and HS (pT+HS) to a mean arterial pressure (MAP) of 30 ± 5 mm Hg for 90 minutes. At the end of HS, recombinant ADAMTS13 was administered at 10 µg/mouse (equal volume of vehicle as control) followed by hypotensive resuscitation with lactated Ringer's (LR) to a MAP 55-60 mmHg for 3 hours. Mice were euthanized and lung tissue, bronchoalveolar lavage (BAL) fluid, and plasma were harvested. Lung histopathology was scored using a 3-point scale, BAL protein was measured as a marker for permeability, VWF binding to collagen (VWF:CB) was measured for VWF adhesive activity. Data are expressed as mean ± SD and analyzed using one-way ANOVA with Bonferroni correction; n= 6/group, *p<0.05 vs shams, **p<0.05 vs pT+HS.

RESULTS. While there were no changes in hemodynamics (Fig 1), mice subjected to pT+HS developed pulmonary hyperpermeability (increasing BAL protein) (Fig 2), lung injury (increased in histopathologic score) (Fig 3) and increase VWF:CB (increased adhesive activity of VWF)(Fig 4), compared to shams, all of which were significantly reduced by recombinant ADAMTS13 (rADAMTS13) administered following pT and hemorrhagic shock.

CONCLUSION: Our results demonstrated that acute pulmonary injury induced by polytrauma and hemorrhagic shock can be significantly reduced by administration of exogenous ADAMTS13. These results suggest that enhancing proteolysis reduces VWF hyperadhesive activity, which we have previously shown to contribute to trauma-induced endotheliopathy. Our data support further investigation into rADAMTS13 as a therapeutic adjuvant for treatment of trauma-induced HS.

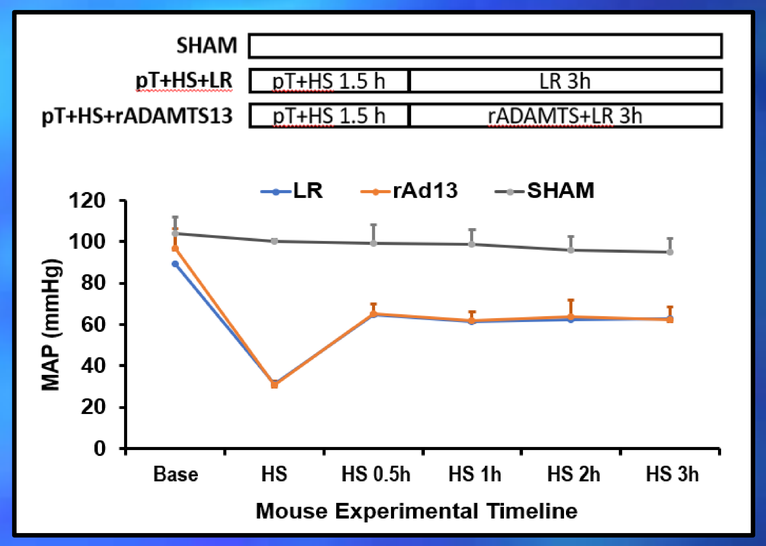

Fig 1. Model and hemodynamics. Mice underwent pT+HS. At the end of HS, mice received recombinant ADAMTS13 (10 µg/mouse) or vehicle followed by hypotensive resuscitation for 3 hours and compared to shams. There were no changes in hemodynamics between the experimental groups.

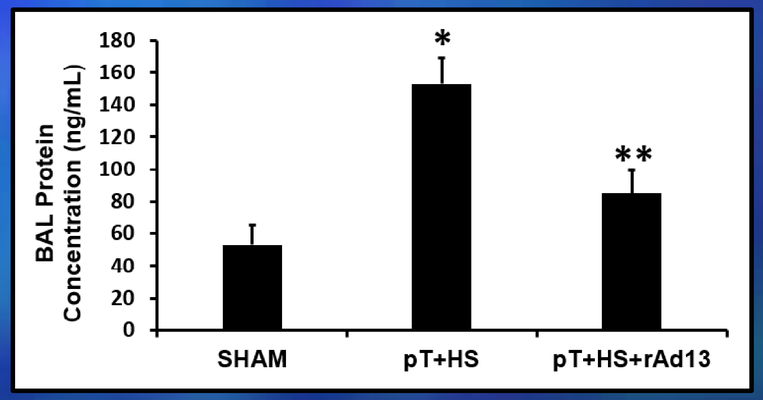

Fig 2. Permeability was reduced by recombinant ADAMTS13. PT+HS mice demonstrated significantly increased BAL protein levels compared to shams which was reduced by rADAMTS13.

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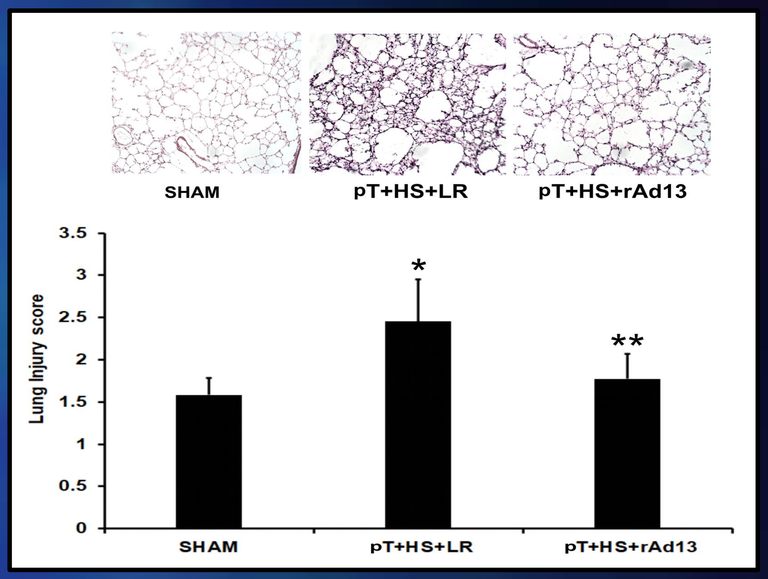

Fig 3. Lung histopathologic injury was lessened by recombinant ADAMTS13. pT+HS mice demonstrated increased lung histopathologic injury compared to shams, whereas rADAMTS13 supplementation significantly reduced lung injury.

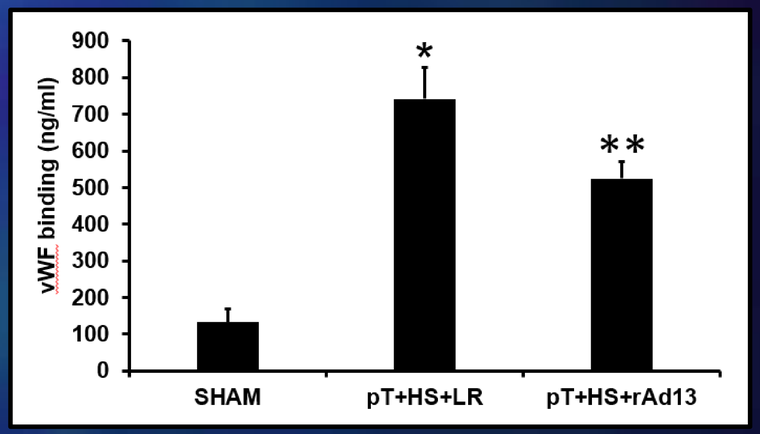

Fig 4. VWF adhesive activity was significantly reduced by recombinant ADAMTS13. pT+HS significantly increased VWF: collagen binding, which was attenuated by rADAMTS13 administration.