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Interleukin-22 attenuates cardiac dysfunction shown by left ventricular pressure characterization secondary to endothelial protection in a rodent model of hemorrhagic shock and resuscitation

Introduction

Hemorrhagic shock (HS) and resuscitation after trauma leads to endothelial glycocalyx (EGx) shedding and trauma-induced endotheliopathy (TIE). Recent studies have demonstrated the glycocalyx-protective effects of IL-22:Fc, a fusion protein of human IL-22 with an Fc immunoglobulin used to extend half-life. The impact of TIE on trauma-induced cardiac dysfunction has not been investigated adequately. In this study, we examine the effect of HS on cardiac EGx damage and test the protective effect of IL-22:Fc on the cardiac endothelium. We hypothesize that IL-22:Fc would mitigate cardiac EGx damage after HS.

Methods

Sprague-Dawley rats (250-350g) were bled to a mean arterial pressure (MAP) of 40 mmHg for 60 minutes. Animals were then resuscitated with same-animal shed whole blood (6ml/kg) resuspended in IV lactated Ringer's to a MAP of 60 mmHg for another 60 minutes. Hemorrhaged and resuscitated (H/R) animals (n=7) were compared to animals treated with 150 ug/kg IL-22:Fc (n=6) at the start of resuscitation. Both groups were compared to time-control sham animals (n=3), which underwent full surgical protocol and cardiac catheterization with exception of hemorrhage/resuscitation. Measured left ventricular (LV) pressure data were analyzed throughout the procedure. Blood samples were collected at baseline and end of resuscitation. Coronary and endocardial tissue was sectioned and imaged using fluorescent microscopy for EGx intensity.

Results

Analysis of LV pressure data at end of resuscitation showed H/R animals had a significantly lower LV end-systolic pressure (LVESP) compared to Sham (68.9 vs 97.2 mmHg; p=0.01). Comparison of contractility (quantified as maximum and minimum change in pressure over time) showed that H/R animals exhibited a decline in dP/dt

max (5728 vs 4167 mmHg/s; $p=0.01$) and an increase in dP/dt min (-6101 vs -3409 mmHg/s; $p=0.01$) from start vs end. H/R caused a decrease in EGx staining intensity compared to Sham (Figure).

While IL-22:Fc did not change LVESP, dp/dt max, and dp/dt min at end of resuscitation compared to H/R, there was no difference in dP/dt max (5686 vs 4586 mmHg/s; $p=0.07$) or dP/dt min (-5795 vs -5060 mmHg/s; $p=0.40$) from start vs end. Additionally, IL-22:Fc-treated animals showed no difference LVESP compared to Sham (80.9 vs 97.2 mmHg; $p=0.14$) at end of resuscitation. EGx loss was reduced with IL-22:Fc treatment in both coronaries and endocardium (Figure).

IL-22:Fc treatment attenuated the change in activated clotting time from start vs end when compared to H/R animals (61.2 vs 155.7; $p=0.01$). IL-22:Fc-treated animals showed no significant rise in blood lactate (1.8 vs 3.0 mmol/L; $p=0.06$) when compared to H/R animals (1.8 vs 4.2 mmol/L; $p<0.001$).

Conclusion

Trauma-induced endotheliopathy occurs in cardiac tissues in response to H/S. IL-22:Fc treatment during resuscitation protects against H/R-induced glycocalyx shedding and preserves cardiac function, suggesting it may be a potential therapy in resuscitation of trauma patients.

