Targeting Tie2 restores hemorrhagic shock-induced microcirculatory perfusion disturbances in cremaster and kidney during fluid resuscitation in rats

A.L.I. van Leeuwen^{1,2}, S. Tian^{1,2}, N.A.M. Dekker^{1,2}, P. Van Slyke³, C. Boer¹, C.E. van den Brom^{1,2}

Departments of Anesthesiology¹ and Physiology², VU University Medical Center, Amsterdam, The Netherlands. Vasomune Therapeutics, Toronto, Canada³

Introduction

Hemorrhagic shock (HS) is associated with acute kidney injury (AKI) and increased mortality. Previously, we showed that targeting the endothelial angiotensin/Tie2 system, which is involved in microvascular leakage, reduced HS-induced vascular leakage and restored microcirculatory perfusion in the cremaster. We hypothesized that the Tie2 agonist, vasculotide (VT), also restores renal perfusion as first step in prevention of AKI.

Methods

HS was induced in rats (n=9 per group) by blood withdrawal until a mean arterial pressure (MAP) of 30 mmHg was reached. After 1 hour of shock, rats received VT or its vehicle PBS, followed by fluid resuscitation for 4 additional hours to maintain MAP >50 mmHg (A).

Microcirculatory perfusion was assessed in the cremaster muscle using intravital microscopy (B) and in the kidney using contrast echography (C). Renal perfusion was calculated by multiplying microvascular filling velocity and microvascular blood volume (D).

Results

Characteristics

Figure 2: Mean arterial blood pressure (A), heart rate (B), pH (C) and bicarbonate levels (D) during HS and fluid resuscitation. Data are mean±SD. * p<0.05 HS vs. sham # p<0.05 HS vs. HS+VT

Vasculotide restores HS-induced microcirculatory perfusion disturbances in cremaster muscle

Figure 3: Continuously perfused vessels (A) and non-perfused vessels (B) in rat cremaster muscle during HS and fluid resuscitation. Data are mean±SD. * p<0.05 HS vs. sham, # p<0.05 HS vs. HS+VT

Vasculotide increased microvascular blood volume and renal perfusion 1h following fluid resuscitation

Figure 4: Microvascular blood volume A (A), microvascular filling velocity, β (B) and estimate of perfusion (C) in the kidney during HS and fluid resuscitation. Data are mean±SD, * p<0.05 HS vs. sham, # p<0.05 HS vs. HS+VT

Conclusion

Targeting Tie2 with Vasculotide restored microcirculatory perfusion in the cremaster muscle and kidney following hemorrhagic shock and fluid resuscitation. Future studies will focus on therapeutically targeting Tie2 to prevent acute kidney injury and multiple organ dysfunction following hemorrhagic shock.