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Mechanical Cisternal Occlusion and Subsequent Glymphatic Disruption are Linked to an Acute Decrease in Cerebral Blood Volume Following Subarachnoid Hemorrhage

Tristan Michael Stani BA MD; Jeff Iliff PhD; Zoe Teton; Justin Schultz Cetas MD, PhD
Oregon Health and Science University

OHSU

Learning Objectives

Understand normal Glymphatic function and its possible contribution to cerebral injury following SAH

Introduction

Glymphatic dysfunction has recently been described following experimental subarachnoid hemorrhage (SAH) in murine and primate models. The Glymphatic system is a brain-wide waste clearance system akin to the lymphatic system for peripheral organ tissue. Glymphatics may be an important new therapeutic target against delayed cerebral ischemia following SAH, yet so far there has been little research to explain what contribution if any glymphatic disruption contributes to the overall injury pattern following SAH.

Methods

Treatment groups consisted of aCSF (n=5), autologous blood (n=5) and microbeads (n=7) injected into the prechiasmatic cistern of adult male rats. A cranial window was made over the middle cerebral artery territory and relative cerebral blood volume change (rCBV) was assessed in real time using optical intrinsic signaling. Intracranial pressure (ICP) was assessed using an intraparenchymal pressure transducer. Glymphatic integrity was assessed by injecting 20 µl of Evans Blue dye into the cisterna magna and quantifying brain surface fluorescence.

References

Iliff, JJ et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. Sci Transl Med. 2012 Aug 15;4(147):147ra111

Fig 1A

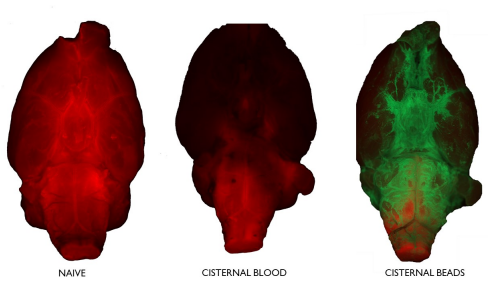
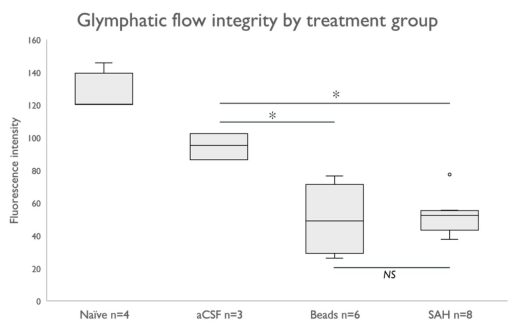
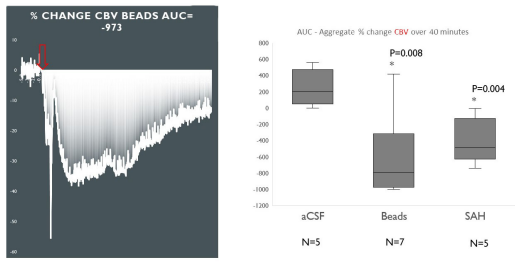


Fig 1B



Beads and SAH treatment groups both produce statistically significant decreases in glymphatic flow integrity compared to aCSF controls. Mechanical occlusion of the subarachnoid space with beads therefore produces glymphatic dysfunction comparable to cisternal microthrombi. This supports the conclusion that glymphatic dysfunction following subarachnoid hemorrhage is due to mechanical obstruction of CSF flow.

Fig 2



Left panel shows representative percent change in rCBV at the time of bead injection and the subsequent 40 minutes. Right panel shows AUC analysis for rCBV profiles across all treatment groups. aCSF controls showed a mild increase in rCBV whereas both SAH and Beads showed a statistically significant decrease in rCBV.

Fig 3A

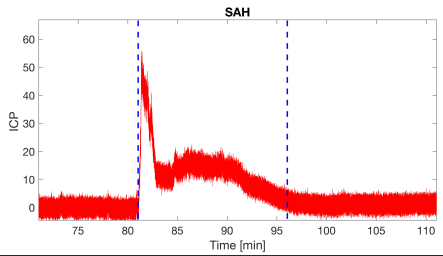
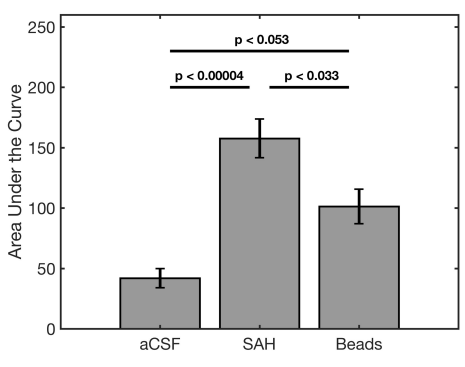


Fig 3B



Results

Microbead and blood injection both produced comparable acute glymphatic dysfunction (Fig 1 A-B). rCBV decreased precipitously in both blood and microbead treatments and remained depressed by 10-40% with variable recovery over 40 minutes of recording (Fig 2 left panel). rCBV area under the curve (AUC) over 40 min was microbeads: negative 544, p=0.009, blood: negative 400, p=0.004 vs aCSF: positive 249 (units % change rCBV x min) (Fig 2 right panel). All treatment groups showed a transient increase in ICP with cisternal injection which returned to near-baseline levels within 10-15 minutes (Fig 3A). AUC of ICP injection profiles were also quantified and compared across groups. The rCBV deficit following bead injections is observed despite only a modest increase in ICP AUC which was not statistically significant compared to aCSF controls (Fig 3B).

Conclusions

Both cisternal microbead and cisternal blood injection produce comparable acute Glympathic dysfunction. Furthermore, in both cases this is accompanied by a significant and comparable deficit in CBV. This phenomenon is not explained by the transient increase in ICP that follows after treatment injections. These results isolate a purely mechanical effect of cisternal microthrombi following SAH and provide initial evidence linking Glymphatic dysfunction to ICP-independent homeostatic mechanisms governing cerebral hemodynamics.