Marked perturbations in CBF and CO2 reactivity in subarachnoid hemorrhage

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Target Audience: Neurologists and neuroscientists in experimental subarachnoid hemorrhage

PURPOSE: Subarachnoid hemorrhage (SAH) is a medical emergency. Vasospasm is a hallmark of human SAH and needs to be treated promptly.[1] However, the effects of SAH on cerebral blood flow (CBF) and neurovascular coupling are seldom studied. The goal of this study was to investigate the effect of SAH on CBF and cerebrovascular CO_2 reactivity in an established rat model of SAH. Comparisons were made with pre-injection and artificial cerebrospinal fluid injection (ACSF).

METHODS: Male Sprague-Dawley rats (n=9 injected with blood, n=9 injected with ACSF, 350-400 g) were studied under 1.2% isoflurane anesthesia. SAH model was created using a modified intracisern autologous blood infusion method.[2] PE-10 tubing with artificial CSF/blood pre-loaded was inserted into and positioned within the cistern magna. MRI was performed on a Bruker 11.7-T/16-cm scanner before and again 1hr, 3hrs, 2 days and 7 days after 300 μL of artificial CSF or blood injected remotely without taking the animal out of the scanner. CBF and hypercapnic challenge fMRI were acquired using typical parameters. The hypercapnic challenge involved exposure to a premixed gas consisting of 5% CO_2 and 95% air. Seven 1.5-mm thick coronal images, FOV=2.56×2.56cm, matrix=96×96. Regions of interest (ROIs) were drawn in cortex across multiple slice images. Open field test for total distance covered was performed longitudinally on the same animals.

RESULTS: Figure 1 shows the time course of CBF from the SAH and ACSF groups. Before injection, CBF of the two groups were not statistically different from each other and their CBF values were consistent with those reported previously in normal rats under identical conditions.[3] In the hyperacute phase (1-3 hrs), CBF dropped substantially after injection in the SAH group and mildly in the ACSF group. On day 2 and 7, CBF of the SAH group recovered significantly but remained lower than ACSF group.

Figure 2 shows CBF responses to 5% CO_2 challenge. In the SAH group, cerebrovascular CO_2 reactivity was markedly reduced at 1 and 3 hrs, gradually recovered on day 2 and 7. By contrast, in the ACSF group, cerebrovascular CO_2 reactivity did not decrease significantly throughout all time points studied and only reduced slightly and non-significantly below the pre injection value.

Figure 3 shows the behavioral scores. In the SAH group, total travel distance was markedly reduced and remained low in all time points studied. By contrast, in the ACSF group, total travel distance was mildly reduced on day 1 and gradually recovered from day 2 to 7.

DISCUSSION: A major finding is that SAH induced marked perturbations of basal CBF and cerebrovascular reactivity immediately after SAH. CBF and cerebrovascular reactivity recovered gradually by day 7. Behavioral score (by open field test) are consistent with MRI findings but the score remained depressed and did not recovered by day 7. A possible explanation that the surgical damage to the injection site could affect animal behavioral or there are changes in the brain that are not detectable by CBF and cerebrovascular reactivity measurements.

Another major finding is that ACSF injection induced slight changes in CBF and cerebrovascular reactivity and the behavioral scores showed better recovery by day 7. A possible explanation is that ACSF also induced intracranial pressure changes, which could affect cerebral perfusion pressure as well as the pressure-CBF autoregulatory relationship somewhat. Intracranial pressure elevation is expected to be transient and subside with CSF reabsorption.

A previous study based on invasive blood flow measurement by radiolabeled technique found similar resting CBF decrease but no difference of the vascular reactivity to hypercapnia in control rats and SAH rats.[4] It is likely that the microsphere technique has lower sensitivity as different animals must be used for pre and post hypercapnic conditions.

CONCLUSION: We found marked hemodynamic disturbance in the brain after subarachnoid hemorrhage, which could contribute to progressive neurological deficits in SAH. Future studies will investigate autoregulation, chronic SAH, and explore treatments.

REFERENCE: 1) Connolly ES Jr, et al. Stroke. 2012; 43:1711. 2) Barry KJ, et al. Stroke. 1979; 10:538. 3) Sicard KM, et al. Neuroimage 2005; 25:850. 4) Diringer MN, et al. J Cereb Blood Flow Metab. 1994; 14:59.

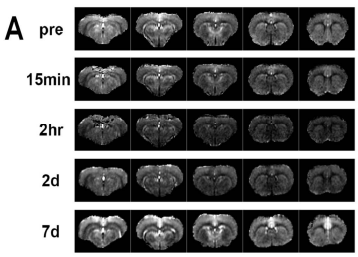

Figure 1. Basal CBF pre and post after artificial CSF (control) and blood injection (SAH).

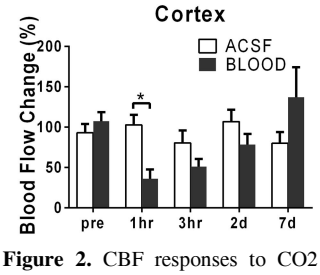

Figure 2. CBF responses to CO2 challenges before and after ACSF and blood iniection.

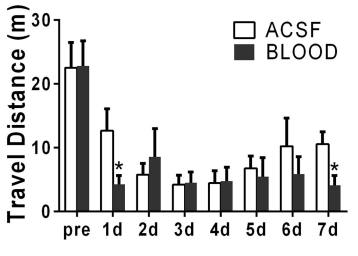

Figure 3. Open field test before and after ACSF and blood injection.