ASSESSMENT OF BLOOD BRAIN BARRIER PERMEABILITY IN THE RAT BRAIN WITH ISCHEMIC OCCLUSION USING DSC-MRI

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Introduction: Blood brain barrier (BBB) disruption following cerebral stroke allows impermeable substances to leak into and out of brain and plays a critical role in brain injury [1]. As the cerebral blood flow (CBF) is closely associated with the permeability surface area product, the increased BBB permeability could affect the quantification of rCBF during stroke[2]. Recently, a graphical Patlak Plot has been used to quantify the blood-to-brain transfer constant (K^{trans}) in a rat model of stroke[1, 3]. To account for the leakage of contrast agent (CA) in cerebral tumors and stroke, different approaches have been proposed[4, 5, 6], because ignoring CA leakage could bias parametric estimates of hemodynamic parameters[5, 6]. In the present study, serially acquired T_2* weighted images were used to assess the BBB permeability in a rat model of stroke. CA extravasation in brain parenchyma was examined by measuring the spatial distribution space of the CA via uncorrected and corrected regional blood volume (rCBV) maps.

Materials and Methods: Permanent MCAo was induced by the intraluminal suture MCAO method as described elsewhere[7, 8]. Five vehicle treated (1% BSA in PBS) [7, 8] male Sprague–Dawley rats (n=5, 250-300 g) were anesthetized with 2% isoflurane during the surgery or 1-2% during MRI scans. Heart rate, respiratory rate, SpO_2, and body temperatures were continuously monitored during surgery and MRI scanning. MR data were acquired with T_2W (TR/TE=2500/11ms, slices=15, NEX=2, FOV=30mmx30mm, thickness=1mm, and matrix size=128×128) and perfusion weighted-MRI using a single-shot gradient-echo EPI (TR/TE =600ms/10 ms, matrix size=128x128, thickness =1.0 mm, measurements= 400, slices =5, total scan time of 86s) on a Bruker 7T scanner. The CA gadoversetamide (Optimark, Mallinckrodt Inc., St. Louis, USA, 0.2mM/kg) was injected *via* a tail vein. Data acquired on Day 2 (48 hours post occlusion) were analyzed using the corrected CA leakage model as detailed elsewhere[4] to examine the BBB permeability. Region of Interest (ROI) was manually drawn by setting the threshold about 5% of blood volume in a single slice with the largest cross-section of the lesion. Data were analyzed with Image J plugin (https://dblab.duhs.duke, NIH.gov/ij).

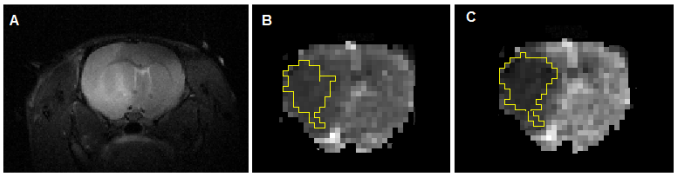

Fig.1. Representative images of **A**) T_2WI, **B)** uncorrected rCBV map, and **C**) corrected rCBV map after pMCAo at 48 hr. Yellow lines represent the spatial distribution space of contrast agent.

Results: A typical T_2WI image and uncorrected and corrected rCBV maps at 48 hours (hr) post stroke is shown in Fig 1. The spatial distribution of CA assessed by uncorrected and corrected rCBV maps in ischemic region at 48 hr post stroke is illustrated in Fig 2. The spatial disruption space of CA assessed by a corrected rCBV map was significantly different (51.0± 9.26 mm^3 vs. 40.60±8.57 mm^3, $p<0.05$) from the uncorrected rCBV map, suggesting that a leakage space grew by about 20%. The increasing spatial distribution space of CA in corrected rCBV map indicates increasing BBB permeability after pMCAo at 48 hr. Of note, extravasation of CA inside the ischemic damaged areas may differ due to tissue heterogeneity (*i.e.,* ischemic core and penumbra). Significant decrease of ischemic region rCBF value on Day 2 (the ratio of lesion to the contralateral side rCBF: 30.43± 3.93 % *vs*. 5.57± 3.05 %, $p<0.05$) could be associated with increased vascular permeability.

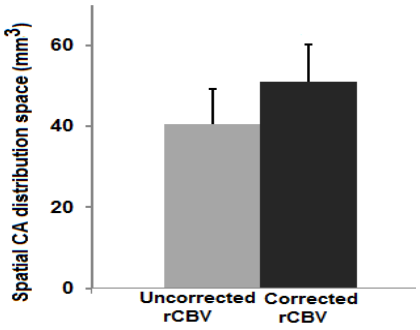

Fig.2. Plot of the spatial distribution space of CA assessed by uncorrected and corrected rCBV maps at 48 hr after pMCAo. Data represent the mean ± standard error (SE).

Discussion and Conclusion: A leakage corrected model[4], which accounts for the amount of tracers that flow through the injured brain regions during the acquisition of perfusion weighted data, can assess the structural and functional integrity of microvasculature. BBB damage that occurs after ischemic insult can lead to intracranial hemorrhage (ICH), which is the most serious complication of thrombolytic stroke treatment[6]. Characterizing the severity and nature of ischemic injury with BBB permeability may help determine an optimal drug delivery and treatment efficacy to the injured brain. This approach may be useful for tracking the integrity of the microvasculature in both animals and humans stroke.

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