Discrimination of Ischemic Tissue Injury and Blood-Brain Barrier Disruption in Acute Stroke: Magnetization transfer MRI with 2D Cluster Analysis, Quantitative Autoradiography, and Histology

R. A. Knight[1], V. Nagesh[1], T. N. Nagaraja[2], J. R. Ewing[1], P. Whitton[1], S. C. Fagan[3], Q. Jiang[1], J. D. Fenstermacher[2]

[1]Neurology - NMR, Henry Ford Health System, Detroit, MI, United States, [2]Anesthesiology, Henry Ford Health System, Detroit, MI, United States, [3]Pharmacy, University of Georgia, Augusta, GA, United States

INTRODUCTION: Improved imaging methods are needed for better identification and discrimination of various pathological changes in brain tissue during and after stroke. This study describes a 2-D cluster plot method that utilizes magnetization transfer (MT) parameters to detect ischemic brain regions with and without acute blood-brain barrier (BBB) disruption in a rat model of transient middle cerebral artery (MCA) occlusion. This model produces BBB injury acutely and hemorrhagic transformation at 24 hours. Area estimates of the total ischemic lesion and regions with BBB opening determined by MRI are compared with similar measurements obtained by histopathologic and quantitative autoradiography (QAR) methods, respectively.

METHODS: Transient ischemia was induced in male Wistar rats (n=20) by intraluminal suture occlusion of the MCA and withdrawal of the occluding filament after 3 hrs. All MRI studies were performed at 7 Tesla. MRI measurements of MT parameters [including M_0, M_{0sat}, T_1, T_{1sat}, K_{for} and the MT ratio] were obtained before and shortly after reperfusion using a gradient-echo sequence[1]. After the completion of MRI studies, the rats were infused with ^{14}C-labeled Gd-DTPA and then sacrificed. Tissue sections were prepared for QAR assessment of areas with BBB disruption and histological evaluation of lesion size. MRI data were analyzed using a 2D-cluster plot of K_{for} vs. T_{1sat} to segment the ischemic areas into those with and without BBB damage. The individual tissue signatures identified from the various clusters were then transposed back onto the original images for anatomical reference and area measurements of abnormal regions. Lastly, these MT-defined areas were compared with estimates of the total area of ischemic injury from histology or BBB damaged areas from QAR. All area estimates are expressed as percentage of the ipsilateral hemisphere (±s.d.) and significance was inferred for $p \leq 0.05$.

RESULTS: The 2D MRI cluster plot analysis yielded different clusters of pixels that corresponded with distinct forms of tissue damage (Figure). Opening of the BBB occurred in the pre-optic area and/or caudate-putamen of all rats and was identified by both MRI MT cluster analysis and QAR methods. Ischemic tissue injury without BBB damage was identified by another cluster and the total area of ischemic injury was obtained by summing the ischemic regions with and without BBB opening (Table). The total area of the ischemic lesion was confirmed by histological assessment. The size and location of the BBB leakage areas identified by MRI were in good agreement with the QAR results (p=0.946). Similarly, the total area of MT defined ischemic damage agreed well with that found by histology (p=0.847).

CONCLUSION: Regional differences in the physiological response to cerebral ischemia can be identified by quantitative MT weighted imaging. These results suggest that MT based MRI provides a more complete description of tissue damage than other currently available methods for imaging cerebral ischemia by identifying areas of early BBB injury in addition to lesion size. Our findings suggest that stroke patients with abnormal BBB MT signatures are potentially at risk of further deterioration of BBB function that could evolve to hemorrhagic transformation.

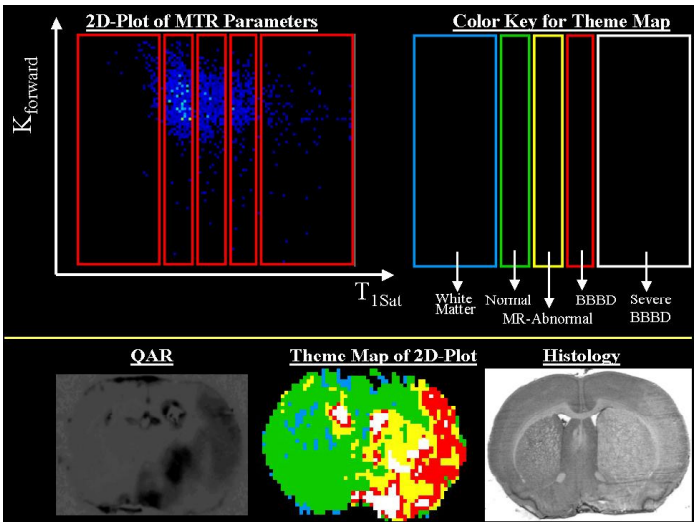

Figure: The top panel shows a 2D cluster plot (left) of K_{for} vs. T_{1sat} from a representative rat at approx. 2 h after reperfusion with the corresponding color key (right). The lower panel shows the theme map from the 2D plot of K_{for} versus T_{1sat} (center), a QAR image showing acute BBB leakage (left) and the ischemic lesion area from histology (right).

Method	Percent area of BBB damage (mean ± s.d.)	Percent of total lesion area (mean ± s.d.)
MRI	9.11 ± 7.70	20.82 ± 8.21
QAR	8.77 ± 7.24	
Histology		20.32 ± 8.27

References:

1. Ewing JR, et al.: In Proc 4th ISMRM (1996);3:1660.