Pixel-by-Pixel Comparisons of Cerebral Blood Flow and T1sat Measured by MRI and Blood-to-Brain Transfer of 14C-Gd-DTPA by Quantitative Autoradiography in a Rat Model of Ischemia.

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INTRODUCTION: Immediately after occluding a cerebral artery, blood flow (CBF) drops precipitously in the downstream microvascular system, and the delivery of nutrients and the removal of metabolic byproducts is severely compromised. This leads to damage of the neurons, glia, and microvessels within the ischemic tissue. Depending upon the time and degree of reperfusion, this injury may subsequently be abated or exacerbated. Often during ischemia and/or reperfusion, blood-brain barrier (BBB) permeability increases (BBB opening), and vasogenic edema develops in areas of BBB opening that have sufficient blood pressure and flow. Both changes are detrimental and increase the rate of mortality after ischemic stroke. Accordingly understanding the roles and interaction of CBF changes, BBB opening, and cerebral edema formation in the initiation and progression of stroke is essential to therapeutic intervention. The purpose of the present study was to test the hypothesis that at least one of the magnetization transfer (MT) parameters is correlated with both CBF and BBB permeability changes in a rat model of reversible cerebral ischemia and that this MT parameter might be a useful, minimally invasive procedure to include when assessing ongoing tissue pathophysiology and treatment in stroke patients.

METHODS: Transient focal ischemia was induced in six male Wistar rats by intraluminal suture occlusion of the middle cerebral artery; three hours later reperfusion was initiated by withdrawing the filament. All MRI studies were performed in a 7 Tesla, 20-cm bore magnet, 4 hours post-ictus. Cerebral blood flow (CBF) was estimated using arterial spin labeling with a variable tip-angle gradient-refocused imaging technique [1]. Rapid estimates of T_1, T_{1sat} (T_1 under an off-resonance saturation of the macromolecular pool), K_{for} (apparent forward rate constant) and MTR (magnetization transfer ratio) maps were obtained from composite images using TOMROPS (T1 by multiple read of pulses) [2]. MTC images were acquired from a single 2-mm thick slice (FOV = 32 mm, 128x128 matrix). MTI data was analyzed using a 2D-cluster plot of MTR vs. T_{1sat} (2DS) to segment the ischemic areas into those with and without BBB damage (Figure 1). The individual tissue signatures identified from the various clusters were used to estimate T_{1sat}, CBF and K_i. CBF and T_{1sat} were expressed as ratio of contralateral normal tissue. Immediately after MRI measures, rats were injected with ^{14}C-Gd-DTPA for QAR assessment of BBB permeability. Animals were infused with ~100 µCi of ^{14}C-labeled Gd-DTPA using step-down procedures that maintain a constant plasma tracer level for ~20 minutes. Using established methods, radiotracer leakage was quantified by calculating the blood-to-brain transfer constants (K_i) from the time-course of ^{14}C-Gd-DTPA plasma concentrations and its concentration in brain tissue determined by QAR [3].

RESULTS: Abnormally high T_{1sat} values indicative of tissue damage grouped into several distinct, well-separated columns along the x-axis of the 2DS (Figure 1). In all six animals BBB damage (BBBD) was identified by 2DS and confirmed by QAR. The mean ± SD in BBBD regions was 1.625 ± 0.118 for T_{1sat} ratio, 0.63 ± 0.125 for CBF ratio, and K_i was $5.42 \times 10^{-3} \pm 1.91 \times 10^{-3}$ ml/g/min. Parametric measures of BBB opening were analyzed and tested for correlation. CBF, K_i, and T_{1sat} were highly correlated (Table). For significant edema formation and flow, two conditions are necessary, (i) the BBB must be open and (ii) blood flow and pressure within the leaky microvessels must be sufficient to drive filtration. Both of these conditions likely contribute to T_{1sat}, which may explain the high degree of correlation between CBF and T_{1sat}.

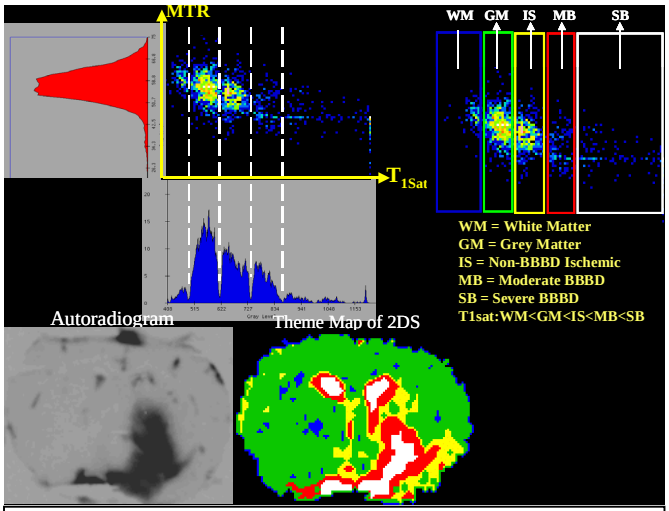

Figure 1: Top left panel shows 2D cluster plot of MTR vs T_{1sat} with histograms displayed along the corresponding axis, color key is in the top right panel. The lower panels show the theme map generated from 2DS (center). The red and white areas correspond to BBB leakage regions, these are in good agreement with dark region of the QAR image.

Parameters	Correlation *r*	Significance *p*
CBF *vs.* T_{1sat}	0.97	0.001
CBF *vs.* K_i	0.82	< 0.05
T_{1sat} *vs.* K_i	0.8	0.05

Table:Correlation of parameters in BBBD areas

SUMMARY: Significant correlation between T_{1sat}, K_i, and CBF validates T_{1sat} as a surrogate for characterizing BBB opening. This supports our hypothesis and suggests that characteristic quantitative T_{1sat} changes can be used to accurately and non-invasively detect the sites and degree of BBB opening.

References:

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