Susceptibility Weighted MRI for Detection and Staging of Angiogenesis After Stroke in Rats

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Introduction: Neurorestorative therapy improves functional recovery in experimental stroke[1,2], which may be related to therapy induced angiogenesis[1-3]. However, noninvasive tools for direct detection and staging of angiogenesis are still under development. We believe our data demonstrate for the first time that high-resolution susceptibility weighted imaging (SWI) incorporating phase information can be used to detect and stag the progress of angiogenesis after stroke.

Methods: Male Wistar rats (n = 6) were subjected to embolic stroke and given sildenafil starting at day 1 and continuing daily for 6 days after stroke. MRI measurements were performed on day 1 and then weekly for 6 weeks. MRI measurements were performed with a 7 T, 20cm bore, Magnex superconducting magnet equipped with a 20 G/cm, 12cm bore gradient insert. SWI, T_1, T_2, and blood-to-brain transfer constant (K_i) of Gd-DTPA were used to characterize biophysical changes in vascular reorganization after stroke. T_1 was measured using the TOMROP Look-Locker (L-L) sequence[4]. K_i, was measured using dynamic L-L T_1 and constructed using Patlak plot methodology[3]. SWI was measured using high resolution (125 x 125 x 250 μm), fully velocity compensated 3D with optimal TE to make the phase of deoxygenated blood to $-\pi$[5]. Signal processing in NMR (SPIN) software was used to combine magnitude and phase information of SWI to maximize negative signal intensities in regions containing deoxygenated blood[5]. To detect angiogenesis, brain sections were either immunostained using endothelial barrier antigen (EBA) or imaged by laser scanning confocal microscopy (LSCM) after injection of FITC-dextran.

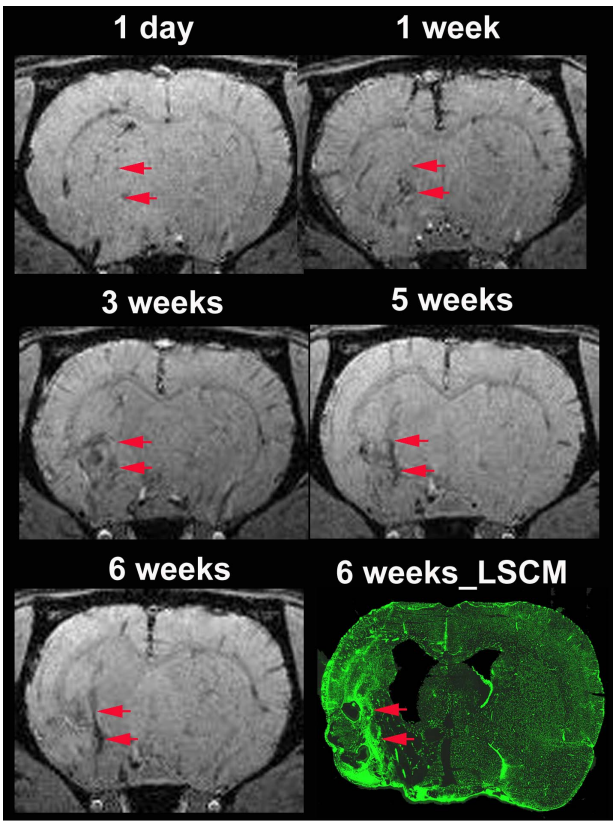

Figure 1. SWI characterization of the evolution of vascular remodeling in the rat brain after treatment of stroke.

Results: SWI revealed dark areas along the ischemic boundary, where the density of EBA immunoreactive vessels increased significantly (594 ± 75 mm^2; p = 0.001) compared with homogeneous tissue of the contralateral hemisphere (371 ± 21 mm^2), indicating areas of angiogenesis. Figure 1 demonstrates that SWI can provide information on new vein formation by following the evolution of vascular remodeling after stroke. Angiogenic regions, determined by increasing numbers of vessels (red arrows) on the LSCM image (bottom right) were clearly identified as dark lines on SWI (red arrows) at 6 weeks after stroke and began to appear 1-6 weeks after stroke. These dark lines were not seen previously (1 day, red arrows), indicating newly formed venous vessels. K_i maps revealed an transient increase in the angiogenic region, which reached a maximum at 1-3 weeks and returned to normal at 6 weeks. The high-pass filtered SWI images exhibited a significant decrease in phase values (p < 0.01) in the ischemic region compared to the homogeneous contralateral tissue from 1 to 6 weeks after stroke.

Discussion: We found that SWI can detect the location and progression of angiogenesis after stroke. Elevated K_i 1-3 weeks after stroke may be a sign of immature vessels that do not have a mature blood brain barrier and leaky. SWI identified functional veins that formed from 1 to 6 weeks after stroke. The combined information from SWI and K_i provided information on the stage of angiogenesis. The increased phase in the ischemic region may be related to increased iron concentration[6] due to its single functional dependence of magnetic susceptibility. The novel finding of this study is that SWI can be used *in vivo* to identify and stage angiogenesis after stroke.

References:

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