USPIO high resolution neurovascular imaging of rat middle cerebral artery occlusion stroke model

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Introduction: Stroke is a leading cause of death and disability and ischemic stroke (e.g arterial occlusion) accounts for most cases. Sildenafil treatment has been shown to promote possibly angiogenesis around the ischemic core in stroke recovery. Susceptibility Weighted Imaging (SWI) and T2* weighted imaging (T2*WI) are sensitive to the venous blood vessel volume and have been demonstrated to be clinically useful in noninvasive imaging of angiogenesis in term of area and T2* ratio change [1-2]. Iron based agents such as ultrasmall superparamagnetic particles of iron oxide (USPIO) have found use clinically in magnetic resonance angiography (MRA) and as macrophage detectors. This has led to the following clinical applications: MRA, studying vascular effects in aging, stroke and multiple sclerosis and assessing the vascular and lymphatic systems. Iron based contrast agents have triple properties in MRI. First, at low concentrations, they act as T1 reducing agents. Second, at higher concentrations, they act as T2 reducing agents. And third, at any concentration, they can also create a local susceptibility effect and therefore create a bulk phase shift. Our new hypotheses are: (1) Because of its sensitivity to both heme and non-heme iron, SWI can be used to detect both arteries and veins with different echo times using USPIO. (2) USPIO along with SWI can be used to detect the development of new vessels post stroke. The purpose of the work is to determine if MRI at 7T with the iron based contrast agent will sufficiently aid in visualization of collateral vessels in the penumbral area of lesions in a rat middle cerebral artery occlusion (MCAO) stroke model.

Methods: The intraluminal filament MCAO stroke model [3] was used in this study. Clinically the MCA is the most frequently embolized artery and reperfusion occurs as a result of recanalization spontaneously, surgically, or pharmacologically. Animals were anesthetized and maintained. A length of 19 mm filaments (with 0.2 mm diameter) was inserted into the right external carotid artery via an arteriotomy with temporary occlusion of the common carotid artery. The filament was then passed up the lumen of the internal carotid artery into the intracranial circulation. The filament lodged in the narrow proximal anterior cerebral artery and blocked the MCA at its origin. The animals awoke 5–10 min after anesthesia was withdrawn. Two hours after MCA occlusion, animals were re-anesthetized, and reperfusion was established by withdrawal of the filament. The USPIO contrast agent was P904 (Laboratory Guerbet, Aulnay, France) with a dose of 0.2mL/kg or 100μmolFe/kg (the P904 molar concentration is 0.5mole/L). Prior to image acquisition, anesthesia was induced by isoflurane (2% v/v) with air to sedate the animals. The T2w, T1w, SWI, MRA, MRI scans were performed on 7T (CLinScan; Bruker, Karlsruhe, Germany). Then P904 was administrated by tail vein with needle of 24G. All MRI scans were then repeated. The SWI imaging parameters were as follows: TR = 50 ms, TE = 5.37, 9.27, 15.12 ms, FA = 20°, with a matrix size of Nx x Ny x Nz = 768 x 768 x 64, FOV=32 x 32 x 16 mm^3, Nacq =2. Imaging time was 45min. Resolution=41.6μm x 41.6 μm x 250μm. MR phase images were first filtered by a 128x128 high pass filter and then projected with their maximal intensity for a 1.5mm thickness using SPIN (Signal Processing in NMR, Detroit, MI, USA). A total 18 Sprague-Dawley rats were studied. The scan time points were baseline, 24h post MCAO, two weeks, four weeks. MRI scans were performed on no stroke (n=1), stroke no treatment (n=5), stroke with sildenafil treatment rats (n=6). Five animals died within 24h after surgery, one by accident and they contributed to normal rat baseline data only. No stroke rat underwent surgery without MCAO. Sildenafil treatment was after 24h stroke subcutaneously daily, total seven days with dose of 10mg/kg and concentration of 1mg/mL.

Results: The first two-animal baseline scans were used to optimize USPIO dose. We found that a third of the initial dose 300μmolFe/kg, i.e.,100 μmolFe/kg, was good enough to show neurovascular structure. Induction of stroke was confirmed with observation of relevant behaviors including the tendency to walk in circles. There were four severe, two mild stroke rats in the treated group, and two severe, three mild rats in the untreated group. SWI shows clearly the presence of newly developed vessels near the periphery of the ischemic core in sildenafil treated severe stroke animals two-weeks after MCAO (Figure 1) but not in mild stroke animals. We also observed several hemorrhages in ischemic cores for severe stroke animals. Each hemorrhage was often near by a large vessel.

Conclusion: Although USPIO reduces intensities of blood vessels therefore contributes negative contrast in magnitude image, it increases blood vessel phase contrast and contributes to positive contrast in phase images. USPIO high resolution SWI provides a way to visualize angiogenesis in rat MCAO stroke model.
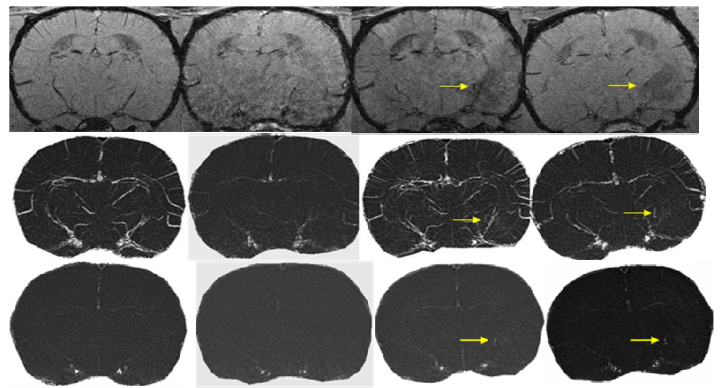
Fig.1. SWI magnitude and phase images (top/middle) with USPIO and phase images without USPIO (bottom) of a Sildenafil treated rat at four time points (from left to right): baseline, 24h post MCAO, 2 weeks and 4 weeks. A newly developed vessel (yellow arrow) around the edge of the ischemic core (dark area) shows up as a black spot in the SWI magnitude image two weeks after MCAO. It shows up as a short white line in the SWI phase images, (six-slice MIP with 1.5mm thickness).

References: (1) Jiang et al. NeuroImage, 28:698, 2005. (2) Ding et al. Stroke, 39:1563, 2008. (3) Ding et al., Behavioural Brain Research 132:29, 2002.