Validation of T2* Weight Signal Change of Oxygen Challenge as a Potential better Penumbra Estimation

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INTRODUCTION Mismatch of diffusion/perfusion by MRI has been used as an estimate of the ischemic penumbra, but there are large parts of the mismatch region appear not to at risk, even though they may contribute to functional impairment (1). It was also reported that some of the apparent diffusion coefficient (ADC) reduction area can be salvaged by early reperfusion. It is essential to find a method to more acutely distinct salvageable tissue from irreversibly damaged tissue. In a permanent middle cerebral artery occlusion (MCAO) model, we demonstrated that T2* weighted (T2*W) signal change induced by 100% oxygen challenge (OC) showed the potential to reflect the metabolic status of tissues (2, 3). It was found that the diffusion/perfusion mismatch region showed higher than normal T2*W signal increase during OC and some ADC reduction area showed lower than normal but significantly higher than ischemic core positive response. We hypothesized that those tissues are more amendable to treatment and T2*W MRI of OC has the potential to better approximate penumbra. To validate this hypothesis, T2*W MRI associated with OC was used to study a group of transient (45-min) MCAO rats. Standard perfusion and diffusion MRI was also performed to identify perfusion-diffusion mismatch. Final lesion determined by T2 weighted imaging was correlated with OC responses.

METHODS Male Sprague Dawley rats (250-300g, n=5) were subjected to 45-min MCAO (4). Rats breathed spontaneously under ~1.2% isoflurane in air. Body temperature and respiration rate were continuously monitored and maintained within normal ranges. OC experimental paradigm was: 1 min OFF, 2 mins ON, 5 mins OFF, 2 mins ON and 1 min OFF, 720 repetitions in total. OC response percent change maps were calculated.

MRI was performed on a Bruker 7T/30cm scanner. A surface coil (2.3-cm ID) with active decoupling was used for brain imaging and a neck coil for perfusion labeling. CBF (cerebral blood flow) was measured using cASL gradient-echo EPI. ADC (apparent diffusion coefficient) was measured using spin-echo EPI. MRI parameters were: single shot, matrix = 96x96, FOV = 25.6 x 25.6mm, seven 1.5mm thick slices, TR=3s, TE=10 ms for CBF and 30ms for ADC, 90^o flip angel. OC T2*W MRI was acquired before and after reperfusion using similar parameters as CBF measure except TR=1s, TE=26ms, 60^o flip angle. T_2 weighted imaging was acquired using RARE sequence at 24hrs post-occlusion to determine the final lesion.

Four ROIs were analyzed: LH (left hemisphere), MM (perfusion-diffusion mismatch), IC (ischemic core) and BZ (border zone of abnormal ADC). ADC and CBF abnormal thresholds of $0.53x10^{-3}$ mm^2/s and 0.3 ml/gram/min (5), respectively, were used to define normal, mismatch and core tissue types.

RESULTS **Figure 1** showed representative ADC, CBF and OC %change maps before and before and after reperfusion. **Figure 2** showed typical ROIs and the T2W imaging at 24hrs post-occlusion for the same animal in **Fig. 1**. Before reperfusion, IC showed negligible response. BZ showed positive response but lower than the LH. MM showed markedly higher response than LH. Group-averaged OC % changes of the MM, BZ, IC were significantly different from LH.

Immediately after reperfusion, ADC almost recovered completely but 24-hrs T2W imaging showed delayed cell death. CBF was restored by reperfusion, with mild hypoperfusion in some area. OC responses after reperfusion did not show significant difference between different regions. By comparing ROIs and 24hrs T2W imaging, MM and BZ defined at 30 mins did not become infarct.

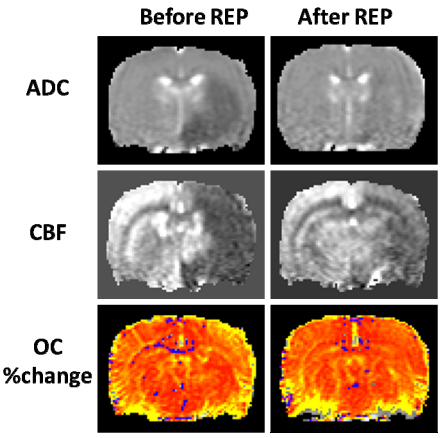

Figure 1 ADC, CBF maps and OC % change before and after reperfusion

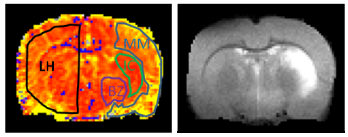

Figure 2 ROIs and 24hrs T2 weighted imaging

DISCUSSION & CONCLUSION The key finding of this study is that reperfusion salvaged tissue that showed large T2*W signal responses to OC. Before reperfusion, the mismatch region, which approximates the penumbra, was metabolically active with restricted blood flow and high oxygen extraction fraction. A higher level of deoxyhemoglobin in blood leads to a higher T2*W signal increase during OC. Similarly, the border zone also showed positive T2*W signal increase during OC, albeit smaller than the mismatch region. Both the mismatch and border zone showed some oxygen delivery and utilization. It is our hypothesis that both the mismatch and border zone may be amendable to treatment. Indeed, 24hrs T2W imaging demonstrated that early reperfusion did salvage these tissues.

ADC and CBF cannot readily distinguish tissue status between BZ and IC. T2*W MRI with OC may offers a novel means to distinguish these tissue types. Treatment time is also important. Early reperfusion may be able to salvage both MM and BZ tissues and relatively late reperfusion may only salvage MM tissues. Experiments with different reperfusion time points are needed to further explore the potential of T2*W MRI of OC. In conclusion, T2*W MRI of OC offers a novel biomarker to identify tissue salvageability that could potential complement conventional diffusion and perfusion MRI in the diagnosis and treatment of acute stroke.

REFERENCE: 1) Kidwell et al, Stroke 2003; 34:2729. 2) Sanrosh et al. JCBFM 2008; 28:1742. 3) Shen et al, ISMRM 2010. 4) Shen et al. JCBFM 2004, 24:280. 5) Shen et al, JCBFM 2003,23:1479. This work is funded by R01 NS045879, SDG-0830293N.