A Validation Study of T2*-Weighted Signal Change of Oxygen Challenge as a Biomarker of Penumbra

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INTRODUCTION T2*-weighted (T2*W) MRI of oxygen challenge (OC) has been used to probe tissue viability in ischemic stroke (1). We have previously shown that T2*W MRI of OC showed unique responses of at risk tissue compared to normal and ischemic core after a permanent middle cerebral artery occlusion (MCAO) in rats (2). Specifically diffusion/perfusion mismatch region showed higher than normal T2*W signal increase during OC. We hypothesized that those tissues are more amendable to treatment and T2*W MRI of OC has the potential to better approximate penumbra. To test 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. T1 effect on OC response was investigated.

METHODS Eight male Sprague Dawley rats (250-300g) were subjected to 45-min transient MCA occlusion using intraluminal suture occlusion method (3). Animals were mechanically ventilated and maintained anesthesia with ~1.2% isoflurane in air. Body temperature, end-tidal CO_2, PaO_2 and heart rate were continuously monitored and maintained within normal ranges. MRI experiments were performed on a 7-T/30-cm magnet. A surface coil (2.3-cm ID) with active decoupling was used for brain imaging and a neck coil for perfusion labeling. Quantitative CBF and ADC (apparent diffusion coefficient) were measured. MRI parameters were: single shot, matrix = 96x96, FOV = 25.6mm x 25.6mm, seven 1.5mm thick slices, TR=3s, TE=10.2ms for CBF and 30ms for ADC, FA = 90°. Oxygen challenge T_2* weighted imaging was acquired using gradient-echo EPI with similar parameters as CBF measure except TE = 26ms and TR =10s. OC experiment paradigm was: 4 min OFF, 4 mins ON, 4 min OFF. OC response percent change maps were calculated. ADC, CBF and OC T2*-W imaging were required before and after reperfusion. And at 24-hr post-occlusion, the animals were scanned again with the same protocol. Quantitative T1 were measured during air and during oxygen inhalation (6 mins) using inversion recovery gradient echo EPI. This was performed only at 24-hr post-occlusion on some animals (n = 3). To demonstrate T1 effect on T2*-weighted signal changes during OC, another OC scan was also performed with short TR (1s). Three tissue types (normal, perfusion-diffusion mismatch and ischemic core) were characterized by using auto-clustering ISODATA method (4) based on 30-min ADC and CBF data. ADC, CBF and OC T2*-W signal percent change of different tissue types at different time points were analyzed. Mismatch tissue was separated to recovered and non-recovered and their OC % change and T2 values at 24-hr were analyzed.

RESULTS **Figure 1** shows the ADC, CBF and OC % change maps before (30-min), after reperfusion (150-min) and 24-hr post-occlusion from one animal. Clustering result and 24-hr T2-weighted image are also shown. Group averaged ADC, CBF and OC% change at three time points of three types of tissues are shown in **Figure 2**.

In perfusion/diffusion mismatch region, OC % change was significantly higher than normal before reperfusion and then changed to close to normal after reperfusion and at 24-hr post-occlusion. Slightly reduced ADC recovered after reperfusion and remained normal at 24-hr post-occlusion. Significantly reduced CBF recovered after reperfusion and show hyperperfusion at 24-hr post-occlusion in part of mismatch tissue.

In ischemic core region, negligible OC response before reperfusion changed to significantly higher than normal and then was negative or close to zero at 24-hr. Significantly reduced ADC transiently recovered after reperfusion and changed back to low again at 24-hr post-occlusion. Significantly reduced CBF recovered after reperfusion and show strong hyperperfusion at 24-hr post-occlusion.

Recovered mismatch tissue showed normal OC% change and T2 at 24-hr (**Figure 3**). In contrast, non-recovered mismatch tissue showed significantly lower OC % change and higher T2.

At 24-hr, baseline T1 increased in the lesion area (**Figure 4 (A)**). In normal tissue, OC induced non-significant T1 change (0.4 ± 3.8%, P>0.05), while in lesion area OC induced strong T1 reduction (-13 ± 5%, P<0.05). At 1s TR, normal tissue showed increased responses as expected, whereas the lesion showed even larger response. At 10s TR, the lesion did not show the large T2*-weighted response, rather some negative responses were detected (**Figure 4(B)**).

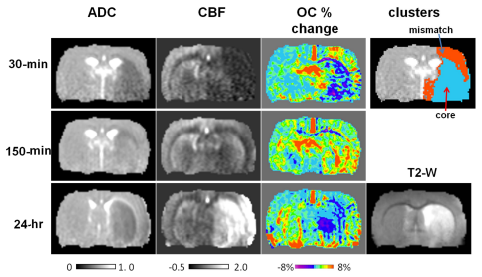

Figure 1 ADC, CBF, OC % change map, clustering result and 24-hr T2W image

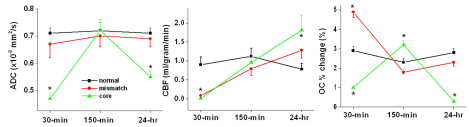

Figure 2 ADC, CBF and OC % changes of normal, mismatch and core tissues at different time points

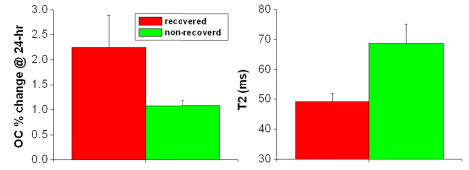

Figure 3 OC % change and T2 values of recovered and non-recovered mismatch tissue at 24-hr.

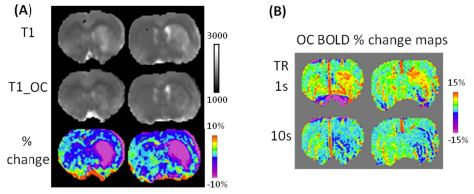

Figure 4 (A) 24-hr T1maps under air and OC and T1 % change. (B) OC BOLD % change maps when TR =1s and 10s at 24-hr post-occlusion.

DISCUSSION & CONCLUSION 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. Normal OC response after reperfusion and at 24-hr post-occlusion indicated they were salvaged, which also indicated by normal ADC. But part of mismatch tissue showed hyperperfusion implied that they might change to lesion later.

The slight negative T2*W signal response at 24-hr post-occlusion in the lesion territory was likely due to dissolved O2 because dead tissue did not metabolize O2, resulting in increased dissolved paramagnetic O2. Negative T2*W response allow us to distinguish dead tissue from normal tissue. **Figure 3** further demonstrates that non-recovered tissue has lower than normal OC response.

The decreased T1 in the lesion under OC contributed to the enhanced OC T2*-weighted response at short TR due to T1 weighting. After removing T1 effect by using long TR, the strong OC T2*-weighted response disappeared (**Figure 4**).

T2*W MRI with OC may offers a novel means to detect at-risk tissue before treatment (higher than normal OC response) and dead tissue at chronic phase (negative OC response).

REFERENCE: 1) Sanrosh et al. JCBFM 2008; 28:1742. 2) Shen et al, Brain Res. 2011 Oct 1. [Epub ahead of print]. 3) Shen et al. JCBFM 2004, 24:280. 4) Shen et al, JCBFM 2004; 24:887.