A Potential Better Estimation of Penumbra Using T2*-Weighted fMRI of Oxygen Challenge

Q. Shen[1,2], S. Huang[1], F. Du[1], and T. Q. Duong[1,2]
[1]Research Imaging Institute, University of Texas Health Science Center at San Antonio, San Antonio, TX, United States, [2]Ophthalmology/Radiology, University of Texas Health Science Center at San Antonio, San Antonio, TX, United States

INTRODUCTION The identification of potentially reversible tissue from irreversibly damaged tissue is of utmost importance for the initiation of treatment strategies to ischemic stroke patients. Irreversible tissue damage and penumbra can be reliably identified by multitracer positron emission tomography (PET) which has severe limitations due to complexity, invasiveness and radiation exposure (1). Mismatch of diffusion/perfusion–weighted MRI has been used as an estimation of penumbra (2). However, it has been reported that large parts of the mismatch region appear not to be at risk, even though they may contribute to functional impairment (3). Inhalation 100% O2 can change tissue deoxyhemoglobin/oxyhemoglobin ratio, especially in penumbra, which is still metabolically active. The deoxyhemoglobin/oxyhemoglobin ratio change can be detected by T2*-weighted MRI. In this study, we investigated the spatial and temporal responses of stroke rats to 100% oxygen challenge (OC) to test the hypothesis that OC responses can be used to identify at-risk tissue.

METHODS Eight male Sprague Dawley rats (250-300g) were subjected to permanent MCA occlusion using intraluminal suture occlusion method (4). Animals were mechanical ventilated and maintained anesthesia with ~1.2% isoflurane in air. Body temperature, ET CO_2, PaO_2 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 (cerebral blood flow) and ADC (apparent diffusion coefficient) were measured using continuous arterial spine labeling gradient-echo EPI and diffusion weighted spin-echo EPI. 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, 90 degree flip angel. Oxygen challenge T2* weighted imaging was acquired using similar parameters as CBF measure except TR = 1s, TE = 26ms, 60 degree flip angel. OC experiment 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. Three tissue types (normal, perfusion-diffusion mismatch and ischemic core) were characterized by using auto-clustering ISODATA method (5) based on ADC and CBF data. Percent change, time to peak (TTP), ADC and CBF values were analyzed for different tissue types. Time to peak was defined as time from one standard deviation above the mean of baseline to 90% of the mean peak value. Profiles of T2* baseline signal intensity and OC percent change were plotted as function of ADC and CBF. The grid size was $0.02x10^{-3}mm^2/sec$ for ADC or 0.12 mL/gram/min for CBF, respectively. A P-value of 0.05 (paired t-test) was taken to be statistically significant.

Fig. 1

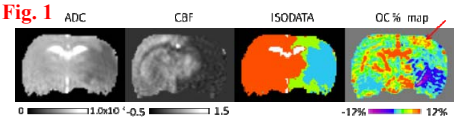
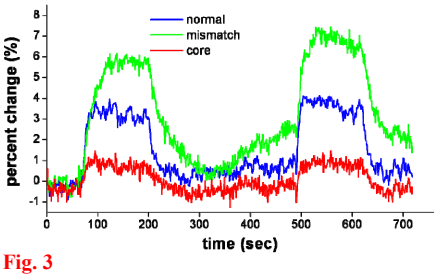


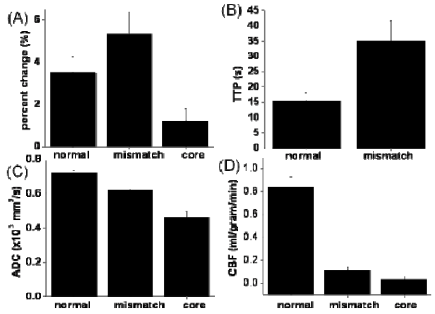
Fig. 2



RESULTS Figure 1 shows representative ADC, CBF map, ISODATA clustering and OC response percent change map. Group-averaged time courses of three regions are shown in **Fig. 2**. Ischemic core region showed negligible response. PWI/DWI mismatch region showed significant higher response compared to contralateral region (arrow in Fig. 1).

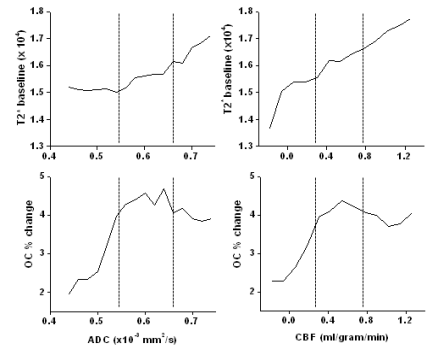
Group-averaged OC percent changes for different regions are summarized in **Fig. 3A**. Group-averaged percent changes were statistic significant different among all three regions ($P<0.05$). OC response of the mismatch tissue showed a much longer time to peak (TTP) than that of normal tissue (**Fig. 3B**). TTP of core region was not analyzed because no significant change was found. Mismatch tissue showed moderately reduced ADC, which was significant lower than that of normal tissue and significant higher than that of core tissue (**Fig. 3C**). CBF of mismatch tissue is slightly higher than but not statistic difference with that of core tissue (**Fig. 3D**).

Fig. 3



Profiles of T2* baseline signal intensity and OC percent change (**Fig. 4**) showed that: 1) baseline signal intensity was lower for lower ADC and CBF, 2) moderate reduction ADC ($\sim0.53\sim0.68x10^{-3}$ mm^2/s) and CBF (~0.3~0.7 ml/gram/min) tissue showed higher OC percent change than normal tissue.

Fig. 4



DISCUSSION & CONCLUSION In normal tissue, the increased oxygen delivery during OC resulted in an increase in the T2*-weighted signal. In the ischemic core, there was no blood flow and oxygen delivery during both baseline and OC, and thus baseline T2* weighted signal was low and there was negligible T2* weighted signal change during OC.

In the "at risk" mismatch, some tissue was still metabolically active but with restricted blood flow. Oxygen extraction fraction and deoxyhemoglobin were higher than normal. Thus baseline T2*-weighted signal was lower than normal. Upon OC, T2*-weighted signal increased in the mismatch was higher than normal because of the smaller denominator. Tissue with enhanced OC responses were above the typical ADC and CBF viability thresholds, further supporting the notion that they are salvageable.

In summary, we detected higher than normal T2*-weighted signal increase during OC in regions surrounding the ischemic core. Tissue with higher than normal BOLD response to OC may be salvageable depending on treatment time, potentially offering another clinically relevant parameter to detect and characterize tissue viability. OC may cause tissue T1 changes and there could be some T1 effects on T2*-weighted signal. Future studies will include the evaluation of T1 effect and OC experiments in transient occlusion group.

REFERENCE: 1) Baron et al. Cerebrovasc Dis 1999; 9: 193. 2) Schlaug et al, Neurology 1999; 53: 1528 3) Kidwell et al, Stroke 2003; 34:2729. 4) Shen et al, JCBFM 2003;23:1479. 5) Shen et al, JCBFM 2004; 24:887.

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