Time-to-Peak of T_2*-Weighted Signal Change of Oxygen Challenge as a Biomarker of Penumbra

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TARGET AUDIENCE Researchers in perfusion imaging, stroke imaging, functional MRI.

INTRODUCTION T_2*-weighted (T_2*W) MRI of oxygen challenge (OC) has been used to probe tissue viability in ischemic stroke (1). We have previously shown that T_2*W MRI of OC exhibited 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 T_2*W signal increase during OC. Tissues with exaggerated OC response was proven to be at-risk and salvageable in a transient MCAO study (3). However, T_2*-weighted MRI of OC challenge in delineating tissue at risk has low contrast-to-noise sensitivity and there are significant false positive and negative pixels, particular from pixels that contain large vessels. In order for this biomarker to be practical, it is necessary to improve its specificity and sensitivity. The goal of this study was to explore the use of the time-to-peak of OC response to further improve the identification of at-risk tissue in ischemic stroke. We analyzed the data of a group of transient (45-min) MCAO rats. Pixel-by-pixel time-to-peak maps were generated. Standard perfusion and diffusion MRI were also performed to identify perfusion-diffusion mismatch. Comparison with OC percent change map was made.

METHODS Eight male Sprague Dawley rats (250-300g) were subjected to 45-min transient MCA occlusion using intraluminal suture occlusion method (4). 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. 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. ADC, CBF and OC T_2*-W imaging were required before and after reperfusion. OC time-to-peak and percent change maps were calculated. The definition of time-to-peak is the time from one standard deviation above baseline to the mean value of the steady state of OC response during the stimulation period.

RESULTS Figure 1A shows 30-min (before reperfusion) ADC, CBF, OC time-to-peak (T_P) maps and T_P map with threshold in a representative rat. Significantly higher than normal time-to-peak was detected in the upper cortical region, better visualized after setting a threshold (mean+2 standard deviations of the normal hemisphere). The region shown delayed time-to-peak corresponded well with the perfusion-diffusion mismatch, where CBF was low and ADC was lower than normal but significantly higher than that of the ischemic core. For comparison, percent change map of OC is also shown in **Figure 1A**. Large percent change responses were often observed in the contralateral normal hemisphere and even in the ischemic core (as pointed by the arrows), creating ambiguity.

The time courses of OC responses of normal and at-risk (with delayed time-to-peak) are shown in **Figure 1B**. To better analyze the difference of time-to-peak, the time courses in **Figure 1B** are normalized from 0 to 1 and shown in **Figure 1C**.

The averaged time-to-peak, ADC and CBF of normal and at-risk tissue are shown in **Figure 2**. The time-to-peak of at-risk tissue was about double that of the normal tissue. ADC and CBF values of the delayed time-to-peak OC responses indicate that these tissues significantly overlapped with the perfusion-diffusion mismatch.

DISCUSSION & CONCLUSION Tissue with delayed time-to-peak corresponded well to the perfusion-diffusion mismatch. This finding indicates oxygen with OC challenge is being delivered to these tissues but at a slower pace, providing unique clinically relevant information, not available with existing imaging techniques. The extent of reduced oxygen delivery can in principle be quantified, which may allow better estimation of the extent of metabolic activity. In conclusion, the time-to-peak OC response provided a higher sensitivity and specificity to identify tissue at risk compared to the magnitude OC response. Moreover, the combined magnitude and time-to-peak OC could achieve better characterization and prediction of ischemic at-risk tissue. This approach could ultimately lead to improvement in the clinical management of acute stroke.

Figure 1 ADC, CBF, OC time-to-peak (T_P) maps and T_P map with threshold in a representative rat at 30-min post-occlusion (before reperfusion). For comparison, OC % change map is also shown.

Figure 2 T_P, ADC and CBF values of normal and at-risk tissues

REFERENCE: 1) Sanrosh et al. JCBFM 2008; 28:1742. 2) Shen et al. Brain Res. 2011;1425:132. (3) Shen et al. JCBFM 2013; Oct 16 [Epub ahead of print]. (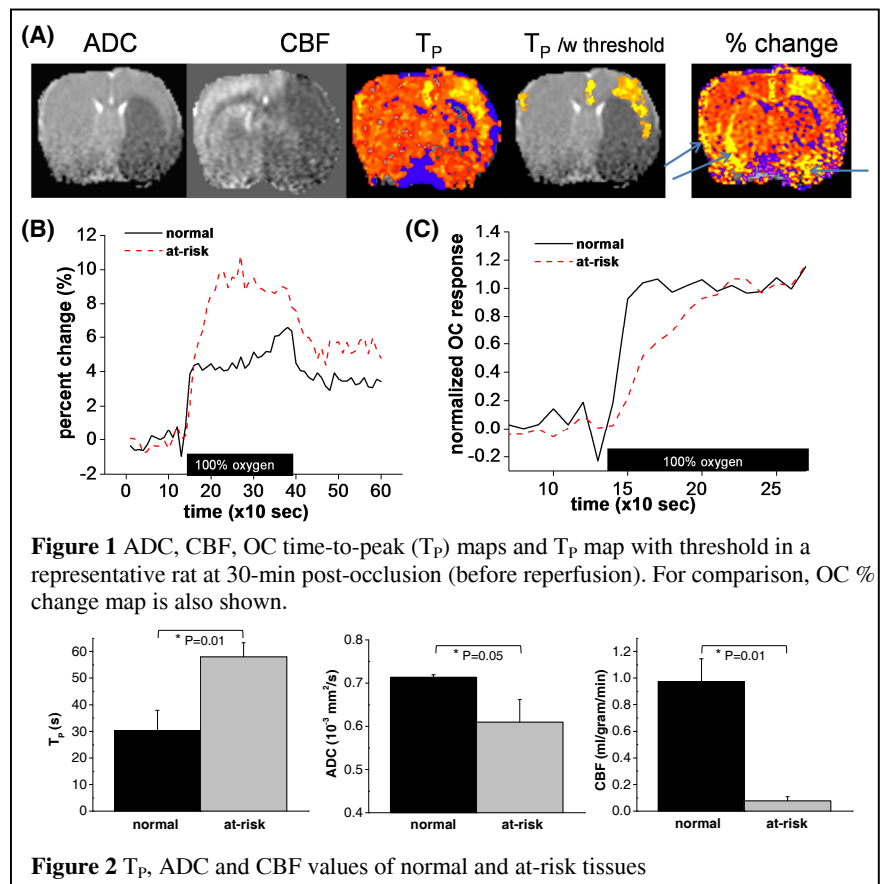4) Shen et al. JCBFM 2004; 24:280.