Time-to-Peak of T2*-Weighted Signal Change of Oxygen Challenge Improves the Identification of Penumbra in Ischemic Stroke

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Target audience: Researchers in perfusion imaging, stroke imaging, functional MRI.

Purpose: 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 T2*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 (TTP) 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 TTP maps were generated. Standard perfusion and diffusion MRI were also performed to identify perfusion-diffusion mismatch. Comparison with OC percent change maps 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*W 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 TTP and percent change maps were calculated. The definition of TTP 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 1 shows 30-min (before reperfusion) ADC, CBF, OC time-to-peak (TTP) and percent change maps in a representative rat. TTP and % change maps with thresholds are also shown. Significantly higher than normal TTP 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 TTP 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 maps of OC with and without threshold are also shown in **Figure 1**. 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 group averaged ADC, CBF, TTP and % change of normal and at-risk tissue are shown in **Figure 2**. The TTP of at-risk tissue was about double that of the normal tissue. ADC and CBF values of the delayed TTP OC responses indicate that these tissues significantly overlapped with the perfusion-diffusion mismatch.

To further compare OC TTP maps with % change maps quantitatively, an additional ROI (blue) in the contralateral hemisphere was chosen. In this type of ROI, significantly higher percent change was shown and in contrast normal or close to normal TTP was shown (**Figure 3**). We suspect that these regions are with large vessels and thus named this type of ROIs 'large vessel'.

The TTP and % change maps of OC after reperfusion (150mins) and 24-hr post-occlusion T_2-W image are shown in **Figure 4**. After reperfusion, both TTP and % change of at-risk tissue went back to normal and the tissue survived, indicated by normal T_2 at 24-hour post-occlusion. The difference between TTP and % change maps is, after reperfusion, the core tissue showed significantly higher % change and only slightly higher but not significantly higher TTP.

Discussion & conclusion: Blood oxygen level-dependent imaging intensity change of OC is complex. The magnitude change only reflects the deoxyhemoglobin concentration difference between two steady states (under air or 100% O_2). It does not reflect the dynamic signal change induced by OC. This dynamic change is determined by not only the deoxyhemoglobin concentrations of two steady states, but also the oxygen delivery rate, which affected by blood oxygenation, CBF and CBV. TTP can be used to quantify this dynamic change. Our results showed that TTP analysis of OC response provided higher sensitivity and specificity to identify tissue at risk compared to the magnitude OC analysis. The extent of reduced oxygen delivery can in principle be quantified, which may allow better estimation of the extent of metabolic activity. Moreover, the combined magnitude and TTP analysis of 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.

References: 1. Sanrosh et al. JCBFM 2008; 28:1742. 2. Shen et al. Brain Res. 2011;1425:132. 3. Shen et al. JCBFM 2014; 34: 169. 4. Shen et al. JCBFM 2004; 24:280.

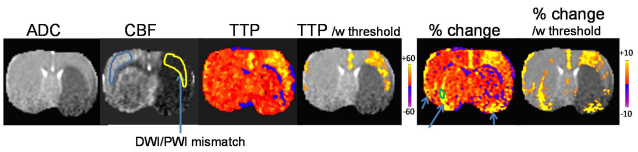

Figure 1 ADC, CBF, OC time-to-peak (TTP) and % change maps in a representative rat at 30-min post-occlusion (before reperfusion). TTP and % change maps with thresholds are also shown.

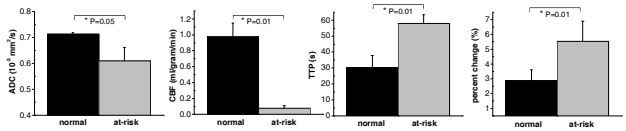

Figure 2 ADC, CBF, TTP and % change values of normal and at-risk tissues

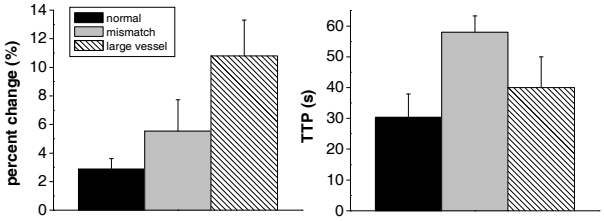

Figure 3 Percent change and TTP of normal, mismatch tissues and large vessel.

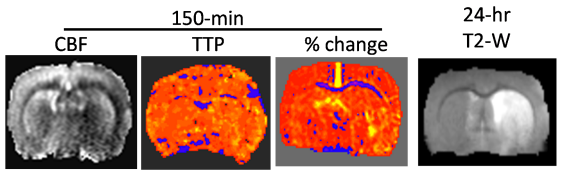

Figure 4 CBF, TTP and % change maps of post-reperfusion (150-min) and 24-hr T2-weighted image.