

Spatial-temporal MRI Responses of Stroke Rats to Oxygen Challenge

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INTRODUCTION Therapy in acute ischemic stroke can only be effective as long as potentially salvageable tissue is present within the brain area affected by the blood flow disturbance. Therefore, the identification of the penumbra and the distinction of this potentially reversible condition from irreversibly damaged tissue are of utmost importance for the initiation of treatment strategies. Irreversible tissue damage and penumbra can be reliably identified by multitracer positron emission tomography which has severe limitations due to complexity, invasiveness and radiation exposure (1). Mismatch of diffusion/perfusion by MRI has been used as an estimate of the ischemic penumbra (2). But 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). Beside perfusion deficit, a marker of metabolism is essential to better define penumbra. In this study, we employed T2*-weighted (T2*W) BOLD fMRI of oxygen challenge (OC) as a mean to probe tissue status associated with acute stroke. This approach was evaluated in permanent middle cerebral artery occlusion (MCAO) in rats. Along with diffusion and perfusion MRI to identify mismatch, we analyzed the spatiotemporal evolution of the BOLD fMRI responses to OC.

METHODS Male Sprague Dawley rats (250-300g, n=6) were subjected to permanent 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° flip angle. Oxygen-challenge T2*W MRI was required using similar parameters as CBF measure except TR=1s, TE=26ms, 60° flip angle.

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 $0.53 \times 10^{-3} \text{ mm}^2/\text{s}$ and 0.3 ml/gram/min, respectively, were used to define normal, mismatch and core tissue types (4). Percent change, time to peak (TTP), ADC and CBF were analyzed in different regions. Time to peak was defined as the time it took to reach from one standard deviation above the mean of baseline to 90% of the mean peak value. A P-value of 0.05 (paired t-test) was taken to be statistically significant.

RESULTS Figure 1 shows representative ADC map, CBF map, typical ROIs and OC %-change map. Figure 2 shows the group-averaged time courses for the four ROI's. IC showed negligible response. BZ showed positive response but lower than the LH. MM, surprisingly, showed markedly higher response than LH.

Figure 3 shows the group-averaged OC %-changes, TTP of OC, ADC and CBF for different regions. Group-averaged OC %-changes of the MM, BZ, IC were significantly different from LH. The relatively longer TTPs in MM and BZ compared to LH indicate slow oxygen delivery as expected. TTP of IC was not analyzed because there was no OC response.

ADC measurements confirmed mild reduction in MM and marked reduction in BZ and IC compared to LH. CBF measurements confirmed marked CBF reduction in MM, BZ and IC compared to LH. ADC and CBF values were not statistically different between BZ and IC.

DISCUSSION & CONCLUSION Under normal conditions, increased oxygen delivery during OC leads to increased T2*W signal. In the ischemic core, no significant T2*W signal increase during OC were observed. The mismatch region, which approximates the penumbra, was metabolically active with restricted blood flow and high oxygen extraction fraction (2, 5). 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, and thus may be amendable to treatment. If indeed the border zone is salvageable, T2*W MRI with OC offers a novel means to identify this tissue. This is particularly important because ADC and CBF values – being not statistically different between BZ and IC – were not able to distinguish their tissue status.

Our findings are in general agreement with Santosh et al (6). It is worth mentioning however that we reported T2*W signal changes in the border zone to be smaller than normal tissue whereas in their study the opposite was found. This inconsistency is likely because different ADC thresholds were used to define the border zone. In that study, ADC at 83.5% of normal was used as the ADC threshold, which could result in the border zone (or part of it) being classified as mismatch. This comparison suggests that the definition of tissue types and ROI used need to be carefully considered and validated.

Finally, we noted that the tissue with higher than normal T2*W signal increase during OC did not completely overlap with mismatch. This observation suggests that T2*W MRI of OC could yield different, but complementary, information from that provided by diffusion and perfusion MRI. In conclusion, T2*W MRI of OC has the potential to better approximate penumbra and warrants further investigation.

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