Dynamic Tissue Fates Tracking in Acute and Sub-acute Phase of a Transient Occlusion Rat Model

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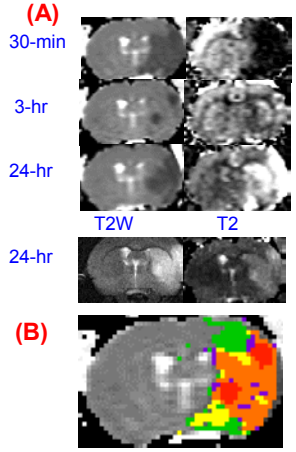
Introduction Diffusion-weighted imaging (DWI) is widely recognized as a powerful tool for the early detection and evaluation of stroke in both animal models and humans. Hyperintense regions on DWI correspond to tissues with a reduced apparent diffusion coefficient (ADC) of water. Similarly, perfusion-weighted imaging (PWI) provides information about the hemodynamic status of brain tissue and detects regions with impaired cerebral perfusion. Clinical reports demonstrated that the impaired perfusion region is typically larger than the lesion detected by DWI early after stroke onset [1]. The difference between the PWI and DWI abnormalities was termed the diffusion/perfusion mismatch, and the DWI lesion usually enlarges over time. The mismatch region may represent potentially salvageable brain tissue with timely and appropriate therapy [2]. Although the "perfusion-diffusion mismatch" is widely observed in acute human stroke, similar observations in animal stroke models have been limited and the temporal evolution of the perfusion-diffusion mismatch in animal models has yet to be systematically investigated. In this study, we utilized quantitative perfusion and diffusion imaging at reasonably high spatiotemporal resolution to investigate, on a pixel-by-pixel basis, the effects of reperfusion in transient focal ischemia in rats during the acute and sub-acute phase. Tissue fates were dynamically tracked in terms of ADC and CBF values and tissue volumes. Hyper-perfusion, found at 24-hr post-occlusion, was discussed.

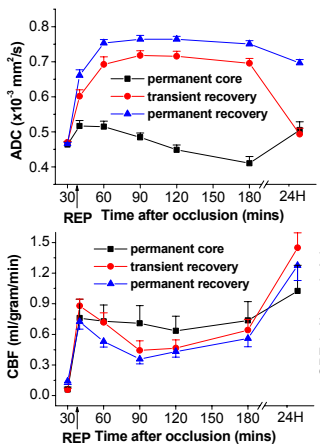
Methods Twelve male SD rats (300-350g) were subjected to 30-min MCAO followed by reperfusion while the animals were in the magnet. MRI data (4.7T) were acquired at 30, 60, 90, 120, 180 mins, ~24 hrs post-occlusion and followed by TTC staining. ADC_{ave} was measured using spin-echo EPI with matrix = 64x64, FOV = 2.56 cm x 2.56 cm, eight 1.5-mm slices, TE = 37ms, TR = 2s, 16 averages, b = 10, 1270 s/mm^2 along each of the 3 principle axes. CBF was measured using the continuous arterial spin-labeling technique with single-shot, gradient-echo EPI, with parameters similar to the ADC measurement except TE = 15ms. At ~24 hrs post-occlusion, T2 was also measured using RARE imaging with two echo times ($TE_{effective}$ =53 and 106 ms) in addition to CBF and ADC. ADC_{av}, CBF and T2 maps were calculated. Maps at 24 hrs were co-registered to 3-hr maps for each animal with a custom-designed co-registration software.

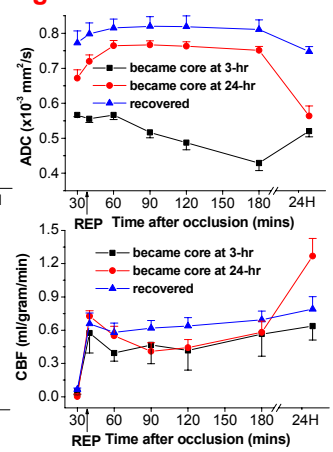
'Ischemic core', 'diffusion/perfusion mismatch' and 'normal' pixel clusters were obtained using an improved unsupervised ISODATA (iterative self-organizing data analysis technique [3]) method based on ADC and CBF maps at 30-min to 3-hr or ADC and T2 maps at 24-hr. The fates of 30-min core and mismatch tissues were dynamically tracked. The core tissues at 30 mins were categorized to three types: 1) permanent core (remained core at both 3-hr and 24-hr), 2) transient recovery (changed to normal at 3-hr but became core at 24-hr) and 3) permanent recovery (changed to normal at 3-hr and stayed as normal at 24-hr). The mismatch tissues were also categorized to three types: 1) mismatch became core at 3-hr, 2) mismatch became core at 24-hr, and 3) recovered where mismatch pixels became normal. ADC and CBF values of these six tissue types and their tissue volumes were tracked as ischemia evolved.

Results and Discusions **Figure 1** showed the ADC, CBF maps at 30-min, 180-min, 24-hr, and T2-weight image at 24-hr of a representative rat. The tissues of different fates were color coded (red: permanent core; orange: transient recovery; yellow: permanent recovery; blue: mismatch became core at 3-hr; purple: mismatch became core at 24-hr; green: recovery where mismatch pixels became normal) and overlaid on ADC map (**Fig. 1B**). More than half core tissues underwent transient recovery and a few was permanently salvaged. Most of mismatch tissues changed to normal and very few changed to core at 24-hr. In this particular example, there were no significant mismatch pixels that changed to core at 3-hr time point.

Figure 2 shows the group averaged (n = 12) ADC and CBF values at different time points of 30-min core pixels. The core pixels started with low ADC and low CBF. The mismatch pixels started with low CBF and mildly reduced or normal ADC. After reperfusion, CBF largely returned to normal and ADC increased. The *permanent recovery* pixels had the largest ADC increase. The ADC of *permanent core* pixels increased slightly and then decreased again. The increase at 24-hr was due to ADC pseudo-normalization not because of recovery as demonstrated by T_2 hyperintensity. The ADC of *transient recovery* pixels increased, although remained lower than normal. The ADC of these pixels decreased at 24-hr. **Figure 3** shows the evolution of the mismatch pixels. The pixels became core at 3-hr had the lowest initial ADC value. The pixels recovered from mismatch essentially had normal initial ADC. Hyper-perfusion was observed in the pixels of *transient recovery* from core and *became 24-hr core* from mismatch. The correlation between 24-hr hyper-perfusion and transient recovery from core and mismatch could imply the correlation between hyper-perfusion and secondary injury. The *permanent recovery* and *permanent core* tissues also showed hyper-perfusion, but which were less significant. The tissues became core at 3-hr and recovered showed normal perfusion at 24-hr.







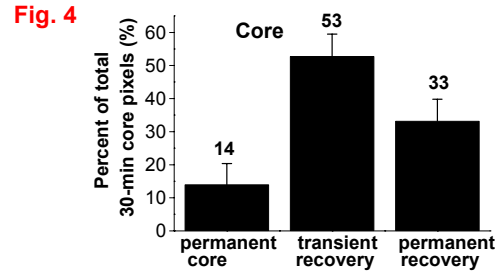


Figure 4 summarized the tissue volume percentage of different fates. More than half of 30-min core tissues underwent transient recovery. About one third core tissues were permanently recovered. More than 70% mismatch pixels were salvaged by reperfusion. And less than 30% mismatch tissues changed to 24-hr core. Very few mismatch tissues changed to core at 3-hr.

Conclusion This study demonstrated an approach to dynamically track and quantify the fates of normal, ischemic and "at risk" pixels in a transient occlusion rat model. This approach provides improved understanding on how ischemia evolves during the critical phase that would be otherwise not possible with ROI analysis or histological studies. Applications include its use to study the effects of neuroprotective drugs on specific tissue fates pixel-by-pixel as well as its use in human studies.

REFERENCES [1] Neumann HT, Stroke 1999; 30: 1591; [2] Barber PA, Neurology 1998; 5: 418; [3] Shen et. al., JCBFM 2004, 24(8): 887.