# Sequential Cerebral hemodynamics and Oxygen Metabolism MRI Study in rats before, during and after Middle Cerebral Artery Occlusion

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## Introduction

During the acute phase of ischemic insult, alterations of cerebral hemodynamics and metabolism are extremely complex and dynamic. Cerebral blood flow (CBF) drops precipitously within a core region, while the CBF in its surrounding regions may progressively reduce as a function of time. Brain tissue within the core region with severely compromised CBF evolves into infarct within a short of period of time, while viable tissue may exist in its surrounding regions hours after the onset of ischemia depending on the severity of CBF reduction and the elapsing time after occlusion[1]. The surrounding hypoperfused yet viable region is usually termed as penumbra. If CBF is not restored before a critical time, the penumbra may be finally recruited into infarction. In this study, sequential monitoring of perfusion and oxygen metabolism using MRI was conducted before, during and after middle cerebral artery occlusion (MCAO) in ischemic as well as in sham operated rats. Differences in tissue 'characteristics' based on hemodynamics and oxygen metabolism are observed for tissues with different outcomes.

## Method

In total, nine rats were studied with approved animal protocols. Cerebral ischemia was induced in-bore using an intraluminal suture MCAO model in six rats and a similar procedure without occluding MCA was performed in the sham operated group (n=3). MR images were acquired on a Siemens 3T Allegra scanner with a small animal birdcage coil. Oxygen extraction fraction (MR_OEF) and CBF were acquired back to back using a 2D multi-echo gradient echo/spin echo sequence[2] and a continuous arterial spin labeling sequence with segmented EPI readout, respectively. MR_OEF and CBF were measured prior to and continued up to 90 minutes post MCAO with an interval of 10 minutes. Immediately after 90 minute MCAO, the suture was withdrawn in-bore from MCA to restore CBF and another measurement of MR_OEF and CBF was acquired. An MR derived cerebral metabolic rate of oxygen utilization index (MR_COMI) was calculated as the product of MR_OEF and CBF acquired successively. 3D volumetric T2-weighted images were acquired at the acute stage and 24 hours after MCAO and were rigidly co-registered using FSL 3.2 (FMRIB, Oxford, UK). In ischemic rats, three ROIs were defined to encompass T2 lesion, peri and contra regions. The T2 lesion ROI was defined as the hyper-intensity regions (> mean + 3 * standard deviation of the signal intensity in the contralateral hemisphere) in the co-registered 24-hour T2W images. Peri ROI was defined as the hypoperfused region that was not recruited into the T2 lesion. The contra ROI is manually outlined as the mirror counterpart in the contralateral hemisphere. In addition, an ROI was manually drawn in the ipsilateral hemisphere in the sham operated rats for comparison. Mean CBF and MR_COMI of the contra ROI at pre MCAO was utilized to normalize the CBF and MR_COMI, respectively, at different time points.

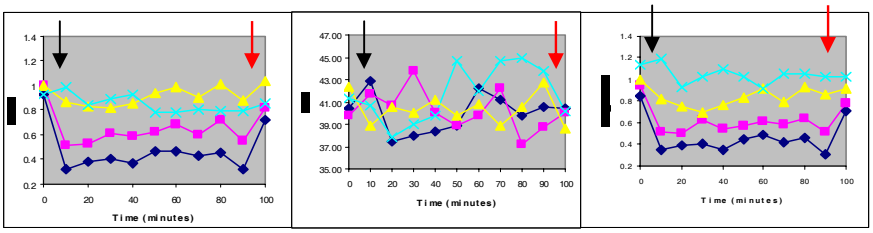


Fig 1. Sequential studies on CBF (left), MR_OEF (middle) and MR_COMI (right) in four ROIs, T2 lesion (dark blue), peri (pink), contra (yellow) and ipsi sham (light blue) before, during and after MCAO. The black and red arrows indicate the time of onset for MCAO and reperfusion.

## Results

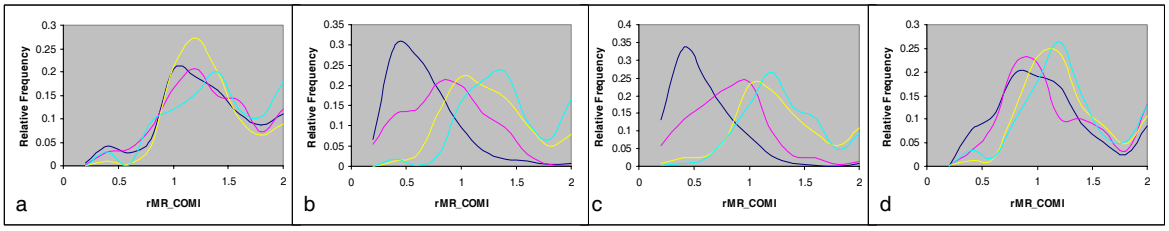


Fig 2. Histogram analysis of MR_COMI in four ROIs, T2 lesion (dark blue), peri (pink), contra (yellow) and ipsi sham (light blue) pre (a) , within 10 minutes (b), 80-90 minutes post MCAO (c) and after reperfusion (d).

Fig 1 demonstrates that following MCAO, the reduction in CBF and MR_COMI are more severe in the T2 lesion ROI when compared to that in the peri ROI throughout the whole duration of MCAO. Conversely, MR_OEF increases in both the T2 lesion and peri ROIs immediately after MCAO and returns to baseline at the later time points. After reperfusion, both CBF and MR_COMI increase in the T2 lesion and peri ROIs. In contrast, CBF and MR_COMI in the contra and ipsi sham ROIs remains stable before, during, and after MCAO. As summarized in Table 1, MR_COMI is statistically different in the T2 lesion and Peri ROIs before reperfusion ($p<0.05$), while a more comparable MR_COMI is observed between these two ROIs after reperfusion ($p>0.05$). The different outcomes indicate that the ischemic injuries in the T2 lesion and peri ROIs are irreversible and reversible, respectively, at the time when reperfusion occurs. Furthermore, the wide tail towards to the right in the T2 lesion ROI histogram (dark blue, Fig 2b) within 10 minutes post MCAO demonstrates that a portion of this region may still be viable at the early stage of ischemic insult. However, as indicated by the narrow peak (dark blue, Fig 2c), the severely injured core region expands and encompasses more voxels as the lesion progresses. The separation between the T2 lesion and peri region is more pronounced at 80-90 minutes post MCAO (Fig 2c) when compared with the early time point (Fig 2b).

| | CBF | | MR_OEF | | MR_COMI | |
|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After |
| T2 lesion | 0.32±0.09* | 0.73±0.18 | 40.6±5.4 | 40.4±3.7 | 0.31±0.12* | 0.70±0.19 |
| Peri | 0.55±0.12 | 0.81±0.22 | 38.7±3.2 | 40.1±4.3 | 0.52±0.14 | 0.77±0.24 |
| Contra | 0.88±0.10 | 1.03±0.23 | 42.7±2.8 | 38.6±3.5 | 0.87±0.09 | 0.92±0.29 |
| Ipsi sham | 0.80±0.13 | 0.86±0.05 | 43.8±0.7 | 40.2±3.1 | 1.02±0.14 | 1.03±0.18 |

Table 1. CBF, MR_OEF and MR_COMI before and after reperfusion. * denotes statistical significance ($p<0.05$) between T2 lesion ROI and peri ROI.

## Discussion and Conclusions

Sequential monitoring of cerebral hemodynamics and oxygen metabolism using MRI before, during and after MCAO revealed different tissue characteristics for irreversible and reversible ischemic injured tissues. Our results are consistent with those reported in the PET literature[1, 3, 4] that the ischemic injury cannot be salvaged when CMRO2 is below 40% of the normal values. In addition, histogram analysis demonstrated dynamic penumbra.

## Reference

1.Powers et al *JCBFM* 1985;5:600. 2.An, Lin. *JCBFM*. 2000;20:1225. 3.Young et al *JCBFM*. 1996;16:1176 4.Giffard C et al *JCBFM*. 2004;24:495