Hemodynamic Features of Early Reperfusion in Reversible Ischemic Rats: A Temporal and Spatial BOLD and CBV Imaging Study at 9.4 Tesla

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Introduction: Four-blood vessel occlusion (4BVO) model has been used to study the cerebral hemodynamic and metabolic features linking to ischemia by using autoradiography and other techniques including MRI [1-3]. However, the temporal and spatial characteristics of these features have not been well investigated, especially during the early reperfusion period. In this study, we applied both multiple-gradient-echo MRI and MION MRI for obtaining high temporal and spatial BOLD and CBV images during the occlusion and reperfusion. Such a study could be capable of differentiating both BOLD and CBV change patterns in different brain regions. Several brain regions of hippocampus, caudate putamen, temporal and parietal lobes were chosen for this study.

Materials and Methods: Twelve Male SD rats weighting 256-340g were used. The BOLD or CBV MR experiments were performed 24 to 48 hours later after the electrical occlusion of bilateral vertebral arteries. The rat was anesthetized and intubated under 2% isoflurane and 60/40 N2O/O2 gas mixture. Both femoral arteries and one side of femoral vein were catheterized for monitoring blood pressure and blood gas, infusion of anesthetics (α-chloralose). The common carotid arteries (CCA) were exposed and surrounded with two plastic occluders (Harvard apparatus, Holliston, MA). The anesthetization was maintained by continuously α-chloralose infusion (25mg/kg/hour) and 60/40 N2O/O2 gas mixture. The rectal temperature was maintained at 37±0.5°C by using a circulating/heating water pad. The blood glucose (GS) concentration and blood gas were tested before and after MR acquisition. The blood pressure was monitored all the time during the experiment. The forebrain ischemia was achieved by inflating the occluders to occlude the CCA, and the occluders were deflated after 12 minutes to resume the blood flow. MR data were acquired at a 9.4 Tesla/31-cm bore magnet (Magnex Scientific, Abingdon, U.K.) with Varian INOVA console (Palo Alto, CA). T2* weighted images were acquired with multi-slice and multi-echo gradient-echo imaging sequence (TR=240ms, TE=8, 16, 24, 32, 40 ms, FOV=1.5×0.75 cm, slice thickness=1 mm, matrix=128×64, pixel size= 117×117 μm, NEX=1, 15s/image). Three slices were acquired for covering the brain structures of interest. The MR observations lasted 50-60 minutes after resuming the blood flow. The BOLD and relative CBV changes at CA1, other hippocampal structures (OHP, including CA2, CA3, CA4 and dentate gyrus), temporal and parietal lobes (cortex), caudate putamen regions were analyzed. Relative CBV (based on MION contrast approach) was calculated. Two-tailed paired t-test was used for statistics.

Results: Physiological changes: (a) BP of pre-, during and post-ischemia was 89.0 mmHg, 107.4 mmHg and 88.0 mmHg, respectively; (b) Blood gas: pre-ischemia: pH=7.48±0.06, PO_2=125.8±19.9 mmHg, PCO_2=33.8±3.7 mmHg, GS=92±5 mg/dl; post-ischemia and 50 min reperfusion: pH=7.42±0.02, PO_2=109.9±18.3 mmHg, PCO_2=39.0±6.4 mmHg, GS=109.9±18.3 mg/dl. The BOLD signal decreased ~9% (no significant difference among the 4 brain areas) after the CCA occlusion. After the releasing CCA, BOLD signal had an overshooting of 8%-20% (peak). There were significant differences in hemodynamic responses among different cerebral regions in the first 22 min reperfusion. The sub-curvature areas of relative BOLD signal in the first 22.5 minutes of reperfusion in 4 measured cerebral regions are different: cortex>caudate putamen>OHP>CA1 ($p<0.05$). However the sub-curvature area of relative CBV show that CA1 >cortex, caudate-putamen and other hippocampal regions, there are no differences among the last three regions. CBV increased up to 56%-68% (peak) during the reperfusion. The BOLD and CBV reached to a relative low level compared to that of pre-ischemia after about 22.5 minutes of reperfusion. The averaged results are summarized in Fig. 1. The peak times of the BOLD and CBV overshooting during reperfusion were various in different cerebral regions (see Table 1). In general, the peaks of BOLD and CBV at cortical area appeared later than CA1, other hippocampal and caudate putamen regions ($p<0.05$). There were no differences among the last three regions. The peak time of CBV appeared later compared to BOLD in all the tested regions, but this difference only reached a statistically significance in the cortical area. The T2* changes are similar to BOLD.

Table 1. BOLD and CBV peak time from the release of the CCA in different regions of the brain

	CA1	OHP	cortex	caudate putamen
CBV (min)	11.8	10.7	14.9	10.7
BOLD (min)	9.2	8.6	11.0	9.8

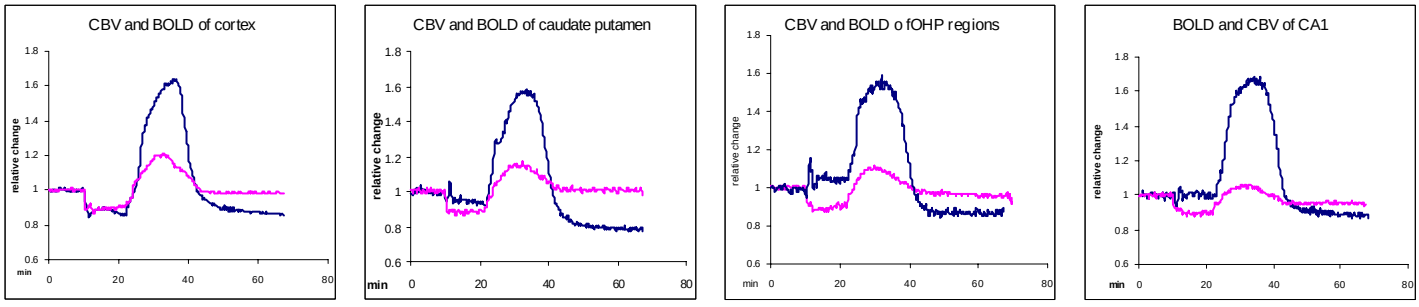

Figure 1. Time courses of relative changes of CBV (blue) and BOLD (pink) in different brain regions. The ischemia started at 10 mins and stopped at 22 mins.

Discussion: The cerebral injury is considered to be the result of early ischemic injury and delayed injury after a period of reperfusion. The present study reported hemodynamic changes in different cerebral regions during four-blood vessel occlusion and early reperfusion. Hippocampal area was reported to be the most severe damaged region in 4BVO model after a relatively long-term reperfusion [1]. In this study, the overshooting of BOLD was found in all the 4 observed regions, CA1 area is the subtlest one (several times smaller than that in the cortical regions), whereas the CBV change during early reperfusion in CA1 area is slightly but significantly larger than other brain regions. And also the peak time of the overshooting in the hippocampal regions is earlier than the cortical regions. This suggests that the damage caused by ischemic insult is heterogeneous in different brain regions. These observations raise two interesting questions: do these early hemodynamic features imply that the hippocampus, especially CA1 area, is the most vulnerable area to ischemia? and what does this mean to the early recovery of metabolism in the insulted brain regions? In order to answer these questions, further investigation, such as direct $CMRO_2$ measurements at the same condition, is necessary. Nevertheless, this study demonstrates that both BOLD and CBV MRI at high fields are sensitive to the pathological changes caused by cerebral ischemia in different brain regions.

Acknowledgments: NIH grants NS38070, NS39043, NS41262, EB00329, EB00513 and P41 RR08079, W.M. Keck Foundation, and MIND institute.

References: *1. Pulsinelli WA, et al. Ann Neurol 11:492-498, 1982. 2. Lei H, et al. MRM. 49:979-84, 2003. 3. Kettunen MI, et al. JCBFM 22: 262-270 2002.*