Functional MRI in Acute Stroke: Correlation with Perfusion and Diffusion Imaging

H. Ren[1], Q. Shen[1], M. Fisher[2], T. Q. Duong[1]

[1]Yerkes Imaging Center, Emory University, Atlanta, GA, United States, [2]Department of Neurology, University of Massachusetts Medical School, Worcester, MA, United States

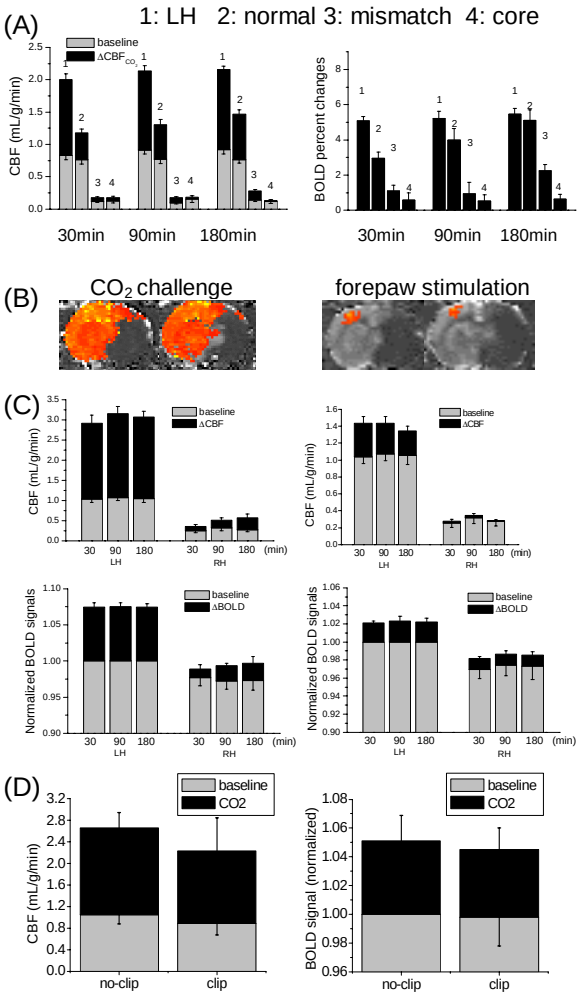
INTRODUCTION The ability to evaluate vascular coupling and functional status following ischemic brain injury during the acute phase would add another useful tool to the stroke imaging protocol. Carbon dioxide is a potent vasodilator and plays an important role in modulating cerebral blood flow (CBF) associated with increased neuronal activity. It can be used to assess the integrity of the neural-vascular coupling in the brain. Forepaw stimulation is widely accepted model for fMRI studies in rats. However, the combined diffusion, perfusion and functional imaging with high temporal resolution during acute stroke has not been reported.

In this study, we developed a protocol for combined diffusion, perfusion and functional MRI to investigate permanent focal ischemia in rats during the acute phase with a 30-min temporal resolution. Quantitative perfusion and diffusion imaging was performed and an improved ISODATA cluster analysis was used to classify normal, ischemic core and "diffusion-perfusion mismatch" tissues. BOLD and CBF fMRI was used to evaluate the hypercapnic and forepaw-stimulation responses in different brain regions as delineated by ISODATA cluster analysis and in the forepaw somatosensory cortices.

METHODS Ten male Sprague-Dawley rats (300-350g) were anesthetized with 2% isoflurane during stroke surgery, the left femoral artery was catheterized and needle electrodes were inserted under the skin of the forepaws. Permanent focal brain ischemia was induced in the right hemisphere using the intraluminal middle cerebral artery occlusion (MCAO) method [1]. Isoflurane was switched to 1.1-1.2% during imaging. Rats breathed spontaneously without mechanical ventilation. Hypercapnic challenge used 10% CO_2. Two forepaws were stimulated simultaneously in series using 6 mA, 0.3 ms pulse duration at 3 Hz, previously optimized for isoflurane anesthetic [2]. In addition, as controls, similar measurements were made on 6 additional rats in which the right common carotid artery (CCA) was remotely clipped/occluded (but without stroke) to study the effect of delayed transit time on fMRI responses (clipping led to labeled spins being supplied only by the left CCA).

Diffusion, perfusion and functional images were acquired with single-shot EPI, matrix = 64x64, FOV = 2.56x2.56cm^2, eight 1.5mm slices at 30, 90 and 180 mins on 4.7T/40cm magnet. ADC_{ave} was measured with TE = 37 ms, TR = 2 s, b = 5, 1200 s/mm^2 along three principle axes separately, and 16 averages. Combined CBF and BOLD measurements were made using the continuous arterial spin-labeling technique, with parameters similar to the ADC measurement except TE = 17 ms and 90 pairs of images. One trial of hypercapnic challenge and three repeated trials of forepaw stimulation were presented (4 mins baseline and 2 mins of stimulation) approximately every 30 mins. A 4-min break was given between trails.

ADC_{ave} images were calculated. CBF images were calculated using baseline data from the fMRI measurements. An improved ISODATA clustering algorithm [3] was used to cluster the tissues to normal, perfusion-diffusion mismatch and ischemic core in right hemisphere based on basal CBF and ADC data. BOLD and CBF fMRI activation maps and percent changes were calculated for each tissue type associated with CO_2 challenge. BOLD and CBF fMRI activation maps and percent changes were calculated for the forepaw somatosensory cortices associated with forepaw stimulation and CO_2 challenge.



RESULTS AND DISCUSSION ISODATA analysis yielded three tissue types in the right hemisphere (RH), namely: normal, perfusion-diffusion mismatch and ischemic core. **Panel A** shows the CO_2 responses of three different tissue types and the left hemisphere (LH) at 3 time points post-occlusion. In the LH, basal CBF was normal and CO_2 fMRI responses were strong (ΔCBF = 1.17~1.24 mL/g/min). In the normal RH, CO_2 fMRI responses were significantly weaker than the normal LH (ΔCBF = 0.47~0.71 mL/g/min), likely due to delayed transit time in the subcortical regions in the ischemic RH. At 180 mins, BOLD responses in the normal RH and the mismatch cluster improved only slightly. In the mismatch and ischemic core, CO_2 responses were essentially abolished at all time points.

Panel B shows representative CO_2-challenge and forepaw-stimulation CBF fMRI maps of a stroke rat at 30-min post occlusion. As expected, only the regions with normal ADC is activated by CO_2 challenge and only the contralateral LH somatosensory cortex was activated by forepaw stimulation. Group-average CO_2 responses and forepaw stimulation responses in the LH and RH somatosensory cortices are shown in **Panel C**. CO_2 and forepaw stimulation induced significant CBF increases in the LH as expected. In contrast, the stimulus-evoked CBF increases in the RH somatosensory cortex were markedly attenuated. Similar results were obtained for the BOLD responses. Interestingly, *percent changes* in the somatosensory cortice (most evident in the CO_2 CBF responses) were comparable between LH and RH due to division by a lower basal CBF at RH. This observation suggests that relative changes may not be a good indicator of neural activity under disease state or pharmacological challenge where basal conditions are markedly disturbed.

As controls, experiments were performed in which the right common carotid artery was remotely clipped/occluded (but without stroke) to study the effect of delayed transit time on fMRI responses. The CO_2 responses in the primary somatosensory cortices were not statistically different between "clip" and "no-clip" conditions (**Panel D**). Similar results were observed for forepaw stimulation (data not shown). These data indicated that the delay transit time did not significantly affect the fMRI responses in the forepaw primary somatosensory cortices but did affect the subcortical structures (data not shown).

CONCLUSION fMRI can be used to track the heterogeneous evolution of functional responses of salvageable *vs.* non-salvageable tissues as delineated by diffusion and perfusion imaging. In the permenant occlusion, functional decline was observed at 30-min post-occlusion. In contrast, there were signficant perfusion-diffusion mismatch at 30-min post ischemia as demonstrated herein and previously [1]. This comparison suggests that functional decline occurred before ADC lesion became apparent and appeared to coincide with perfusion decline. The precise CBF threshold below which fMRI responses are abolished or attenuated remains to be investigated.

References [1] Shen et al., JCBFM 2003, 23:1479. [2] Liu et al., MRM 2004, 52:277. [3] Shen et al., JCBFM 2004, 24: 887.