Prolonged Post-ischemic Hyperperfusion: a Systematic Multimodal MRI Study

Q. Shen[1,2], F. Du[1], S. Huang[1], and T. Q. Duong[1,2]
[1]Research Imaging Institute, University of Texas Health Science Center at San Antonio, San Antonio, TX, United States, [2]Ophthalmology/Radiology, University of Texas Health Science Center at San Antonio, San Antonio, TX, United States

INTRODUCTION Regional hyperperfusion after stroke (1, 2) is a frequent, yet poorly understood, phenomenon. It is unclear whether hyperperfusion harms or helps tissue survival. Prolonged, up to 7 days post-occlusion, hyperperfusion has been noticed in animal stroke model (3). In this study, we systematically investigate the hyperperfusion phenomenon in a 30-min transient middle-cerebral artery occlusion (MCAO) in rats. Multi-parametric MRI including diffusion, perfusion, T_2, T_1, pH-weighted and dynamic contrast-enhanced MRI, and MR angiography, were acquired to characterize post-ischemic hyperperfusion at multiple time points after stroke.

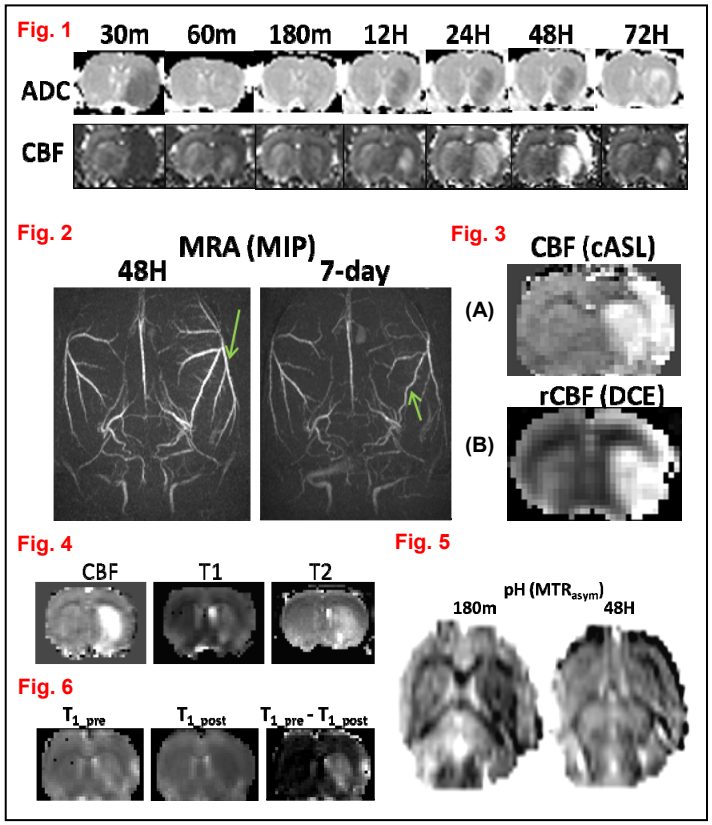
METHODS Ten male Sprague Dawley rats (250-350g) were subjected to 30-min MCAO (4). Quantitative CBF (cerebral blood flow measured using continuous arterial spine labeling), ADC (apparent diffusion coefficient) and MRA (MR angiography using FLASH-3D) were acquired every 30 mins for 3 hrs as well as immediately after reperfusion (acute phase). In addition, T_2 (RARE), T_1 (inversion recovery EPI) and pH (amide proton transfer (5)) changes were measured at 3 hr, 1, 2, 3 and 7 days after stroke. In some animals, blood brain barrier (BBB) leakage was evaluated by comparing T_1 maps before and after intravenous injection of Gd-DTPA, and perfusion was measured by dynamic contrast enhanced (DCE) imaging. MRI experiments were performed on a 7-T/30-cm magnet. A surface coil (2.3-cm ID) with active decoupling was used for brain imaging and a neck coil for perfusion labeling. ADC, CBF, T_1 and T_2 maps were calculated. Relative CBF (rCBF) was calculated from DCE data. pH was analyzed using a magnetization transfer asymmetry parameter MTR_{asym} at the offset of 3.5ppm: $MTR_{asym}(3.5ppm)=100\%x[S_{sat}(-3.5ppm)-S_{sat}(3.5ppm)]/S_0$ (5). MRA was analyzed using maximum intensity projection.

RESULTS Figure 1 shows ADC and CBF maps at different time points of a 30-min MCAO rat. Some hyperperfusion was observed at 3 and 24 hours. Significant hyperperfusion was observed at 24-hrs, peaked at 48-hrs post-occlusion and weakened at 72 hrs post-occlusion. Hyperpefusion was observed in all rats subjected to 30-min MCAO.

Hyperperfusion was corroborated by MRA (**Fig. 2**) and rCBF obtained by DCE method (**Fig. 3B**). MRA at 48-hrs showed thicker and brighter blood vessel enhancement with many smaller vascular branches becoming more apparent in the ipsilateral right hemisphere compared to contralateral hemisphere. MRA at day 7 showed very tortuous vessels. CBF by DCE and by cASL showed essentially identical hyperperfusion territories.

Hyperperfusion was associated T_1 and T_2 increases (**Fig. 4**). pH decreased most significantly around 3 hrs post-occlusion. pH reduction became smaller at 48 hrs (**Fig. 5**). Note that a horizontal slice was imaged to achieve uniform magnetization transfer effect because a surface coil was used.

The difference T_1 image between pre- and post- Gd_DTPA injection at 48 hrs after stroke (**Fig.6**) showed enhancement in the region of hyperperfusion, indicating hyperperfusion is associated with significant BBB leakage. No apparent BBB leakage was detected in the acute phase from 30-180 mins.



DISCUSSION & CONCLUSION The key findings of this study are: 1) highly reproducible prolonged post-ischemia hyperperfusion was observed in 30-min MCAO rat model, 2) hyperperfusion was corroborated by MRA and DCE, 3) hyperperfusion was associated with T_1, T_2 increases, pH decrease in the acute phase, and BBB leakage in chronic phase.

In some human studies, post-ischemic hyperperfusion has been reported to be a harmless and even perhaps beneficial phenomenon (5, 6). In contrast, in most experimental studies (7, 8), post-ischemic hyperperfusion was demonstrated to be not beneficial and even detrimental because it could accumulate by-products (such as free radicals) that result in delayed neuronal damage. Heiss (7) stated that forced reperfusion by reopening of the MCA cannot salvage already irreversibly damaged tissue but may cause additional damage by inducing edema, and that this latter effect may be aggravated by severe and prolonged hyperperfusion in paralyzed vessels. In this and previous (3) work, it was found that the hyperperfusion region is highly correlated with tissues which subsequently became infarcted. While other interpretations are possible, prolonged post-ischemic hyperperfusion herein appeared to be associated with pH reduction in the acute phase which triggered regional vasodilatation and increased blood-brain permeability in the chronic phase (10). In conclusion, hyperperfusion does not appear to salvage tissue. Multimodality MRI investigation helps to gain significant insights into the underlying pathophysiological changes associated with post-ischemia hyperperfusion.

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