Temporal Assessment of Rat Brain Vasculature after Transient Focal Cerebral Ischemia

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Synopsis

The exact mechanisms and physiological significance of angiogenesis in stroke remain obscure. In the present study, the high-resolution mapping of transverse relaxation rate shift was applied to investigate the temporal changes in microvessel size and density in rats subjected to 50 mins of middle cerebral occlusion (MCAO).

Introduction

Angiogenesis plays an important role in stroke patient survival. The association of CBF and CBV with angiogenesis after transient focal cerebral ischemia has been documented [1]. However, the relationship between the changes in angiogenesis and hemodynamics over time is still unknown. High-resolution mapping of vascular function is important for studying the angiogenesis activity in ischemic animal model. CBV obtained from the dynamic imaging technique requires rapid imaging technique that severely compromises the spatial resolution. In addition, CBV reflects the combined effect on the average size and density of microvessels. Thus, CBV alone may not be a reliable indicator of microvessel density or size. Recently, high resolution steady state imaging technique with transverse relaxation shift [2] has been proposed to study the microvasculature of pathological tissue. The parameters of transverse relaxation rate shift, gradient echo-based ΔR_2^* map approximating total blood volume changes and spin echo-based ΔR_2 map reflecting capillary-weight of blood volume, whereas the ratio of ΔR_2^* map and ΔR_2 map is proportional to averaged vessel size, and $\Delta R_2/(\Delta R_2^*)^{2/3}$ is associated with vessel density. The purpose of the present study is thus to apply the steady state method to investigate the changes among blood volume, vessel size and vessel density with high resolution over time in relation to hemodynamics and angiogenesis in a well-defined three-vessel occlusion model in rat.

Material and Methods

Male Long-Evan rats (250 ~ 300g) were subject to transient MCAO for 50 minutes. The rat was anesthetized with isoflurane/air mixture and examined on Pharmascan 7.0 Tesla MR scanner. To determine ΔR_2 and ΔR_2^*, T2-weighted spin echo and T2*-weighted gradient echo sequence were employed and performed before and after the injection of iron oxide (Feridex IV, Berlex Laboratories, Wayne, NJ, USA) with the dose of 30 mg Fe/kg. The post-contrast image acquisition was delayed by 5 minutes for ensuring a steady state distribution of contrast agent in the vascular network. T2 and T2*-weighted MRI were scanned in the same location with a FOV of 2.56 cm, matrix size of 256*128 (zero-filling to 256*256), a slice thickness of 1 mm. T2-weighted MRI was acquired using RARE sequence with a TR of 4000 ms and a TE of 70 ms. T2*-weighted MRI was acquired using FLASH sequence with a TR of 300 ms, a TE of 13 ms and flip angle of 15 degree. All images were acquired at day 1, day 7, day 14 and day 21 after 60 minutes of transient ischemia (n=4 for each time point). Transverse relaxation rate change were given by $\Delta R_2 = \ln(S_{pre}/S_{post})/TE$ and $\Delta R_2^* = \ln(S_{pre}^*/S_{post}^*)/TE$, where S_{pre}, S_{post} and S_{pre}^*, S_{post}^* are the pre-contrast and post-contrast signal intensities for spin echo and gradient echo, respectively, whereas TE is the echo time. Vessel density and size imaging (VDI and VSI, respectively) were derived according to the ratio of relaxation rate shift, $\Delta R_2^*/\Delta R_2$ and $\Delta R_2/(R_2^*)^{3/2}$, respectively, pixel-by pixel using Matlab (MathWorks, Natick, MA, USA).

Results and Dicussion

The representative set of T2-weighted, ΔR_2, ΔR_2^*, VSI and VDI images and their quantitative analyses obtained from a rat subjected to 50 min of transient MCA occlusion at different time points and from a sham-operated rat were shown in Fig. 1 and Fig. 2, respectively. All the parameters in the sham-operated rats were unchanged. ΔR_2 and ΔR_2^* in the ipsilateral cortex, especially in the outer cortical layers, increased gradually from day 1 to day 14 suggesting the increase of blood volume and then slightly decreased at day 21. VDI slightly decreased at day 1 and then gradually increased from day 1 to day 14 suggesting the increase of microvessel density. The significant increase in VSI was noted on day 1 in the ipsilateral cortex which is believed to be related to the vascular dilation and gradually leveled off with control in due course. The increase of CBV at day 1 is mainly due to the increase in vessel size whereas the observed increase at day 14 is mainly owing to the increase in microvessel density.

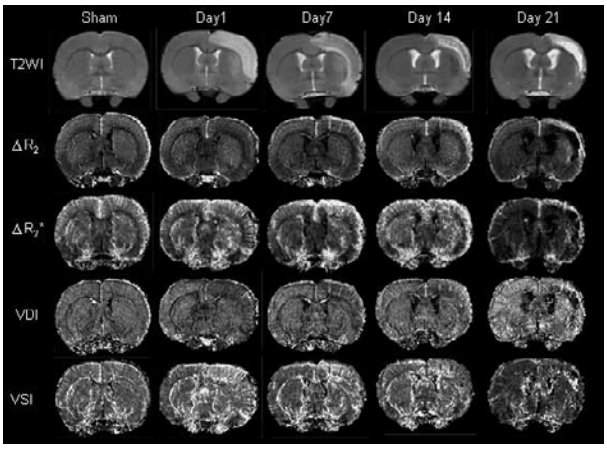

Fig. 1. A representative of T2-weighted images, ΔR_2 maps, ΔR_2^* maps, VDIs and VSIs at indicated time points in a transient MCAO model of 50 mins.

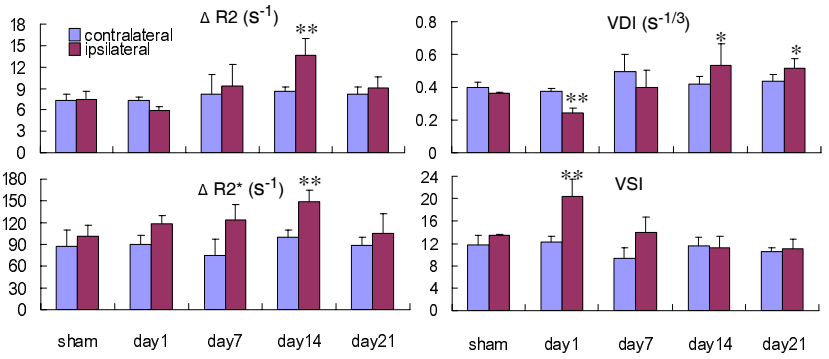

Fig. 2 Temporal changes of ΔR_2, ΔR_2^*, VSI and VDI (mean±SD; n=4;) (*P<0.05; **P<0.01).

Conclusion

The present study demonstrates that relaxation rate shift mapping is a useful method to evaluate the changes of blood volume, vessel size and vessel density over time following ischemia and reperfusion, which could provide more information and new insights into the response of microvascular structure to ischemic insult.

Reference

1. Lin, T.N. et al., *Stroke*, 33:2985-2991, 2002.
2. Dennie, J., et al., *MRM*, 40:793-799, 1998.