Restorative strength of the remodeled vessels after transient focal cerebral ischemia in rats: evaluation with BOLD MRI

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Introduction Vascular remodeling is an important natural defense mechanism to potentially restore oxygen and nutrient supply to the affected brain tissue. The restored perfusion of the ischemic region promotes functional recovery [1]. Nevertheless, whether the remodeled vessels after the ischemic insult function as mature vessels remains to be studied. Functional, mature vessels are capable of supplying brain tissues by increasing blood flow via dilation and then delivering oxygen as well as nutrients to the region. Therefore, understanding the dilatability and oxygenation ability of the remodeled vessels after the ischemic insult may shed light on the restorative strength of the vascular remodeling on the lesion. Hypercapnia and hyperoxia are two inhalant challenges used to alter vascular dilation and oxygenation [2]. In mature vessels, air mixed with CO₂ induces hypercapnia to cause vasodilation and then elevates oxygenation. The level of oxygenation can be further maximized by O₂ with CO₂. It remains unknown whether the remodeled vessels in stroke can dilate, oxygenate, or maximally oxygenate as mature vessels. The goal of this study was to elucidate the functional characteristics (i.e. dilatability and oxygenation ability) of vascular remodeling after ischemia. Such understanding is important for developing treatment strategies that utilizes the vascular restorative process for repairing the injured area.

Materials and Methods Sprague–Dawley rats at 8-9 weeks old were subjected to transient middle cerebral artery occlusion (MCAO) for 60 minutes. All images were acquired in a 7T PharmaScan 70/16 MR scanner with an active shielding gradient. The rats were initially anesthetized with 5% isoflurane at 2L/min air flow. When fully anesthetized, the animal was placed in a prone position and fitted with a custom-designed head holder inside the magnet. The anesthesia was maintained by 2% isoflurane via a nose piece throughout the experiments. To determine R₂⁎ multi gradient-echo (MGE) was performed with the inhalation of air, air+5%CO₂, or O₂+5%CO₂. Acquisition was delayed by 15 minutes after gas transition to allow complete gas exchange. MGE was acquired with a TR of 200 ms, an initial echo of 5 ms, an echo spacing of 5 ms, 12-echo times and a flip angle of 25°, FOV = 2.56×2.56 cm², acquisition matrix = 256×256. R₂⁎ maps were calculated on a pixel-by-pixel basis in MR vision (MR vision Co.). The one with TE = 25 ms was chosen to represent T₂⁎ WI. Hypercapnia (air+5%CO₂) induces dilative oxygenation, and the effects were represented by ΔR₂⁎ maps derived from subtracting the R₂⁎ map of air+5%CO₂ from that of air. O₂+5%CO₂ maximizes oxygenation, and the effects were represented by ΔR₂⁎ maps derived from subtracting the R₂⁎ map of O₂+5%CO₂ from that of air+5%CO₂.

Results and discussion The R₂⁎ map and T₂⁎ WI under air inhalation were used to identify cerebral blood vessels. At day 1 after ischemia, the lesioned cortex had few vessel-like signals and had a high signal intensity on T₂⁎ WI and low R₂⁎ values due to edema (see the first row in Fig. 1). At day 3, the lesioned cortex showed immense vessel-like hypointensities on T₂⁎ WI and hyperintensities on the R₂⁎ map, which provides the evidence of the remodeling of the vasculature (see the first row in Fig. 2). Less hypointensities on T₂⁎ WI and hyperintensities on the R₂⁎ map were observed at day 7, which indicates the regression of the remodeled vessels (see the first row in Fig. 3). No significant changes with time in the contralateral cortex were observed on R₂⁎ maps and T₂⁎ WI. Fig. 1, 2, and 3 present evidence of the functionality concerning the dilatability and oxygenation ability of the cerebral vessels at the three time points. At day 1 as shown in Fig. 1, the scarce vessels on the lesioned cortex (see R₂⁎ map and T₂⁎ WI on the first row) showed no reactivity to the inhalant, regardless of air+5%CO₂ (see R₂⁎ map and ΔR₂⁎ map on the second row) or O₂+5%CO₂ (see the third row). By contrast, the contralateral cortex reacted to both inhalants. At day 3 as shown in Fig. 2, the new vessels resulted from vascular remodeling (see the first row) responded to air+5%CO₂ (see the second row) but not O₂+5%CO₂ (see the third row), indicating that the remodeled vessels were able to dilate with moderate oxygenation but the oxygenation could not be maximized as the mature vessels in the contralateral cortex. At day 7, the regression vessels (see the first row) exhibited a similar response as at day 3 (see the second and third rows). The results show that, while consistent responses were observed in the contralateral cortex and bilateral striatum, the functionality in dilative oxygenation and maximal oxygenation of the lesioned cortex varied with time. Quantitative results are presented in Fig. 4. The dilative oxygenation and maximal oxygenation were low in the lesioned cortex at post-ischemic day 1. At day 3, a significant increase in dilative oxygenation was noticed in the lesioned cortex but the maximal oxygenation became even lower. This indicates that the remodeled vessels were dilatable with moderate oxygenation but could not be further oxygenated to a maximal level. At day 7, dilative oxygenation of the vessels in the lesioned cortex was similarly at a heightened level despite a slight decrease possibly attributed to vessel regression. The level of maximal oxygenation remained low. Our results show that the mature vessels on the contralateral side are able to maximize oxygenation whereas the remodeled vessels in the lesioned cortex lack this ability. Our results reveal distinct functional characteristics of the vessels in the lesioned areas resulting from postischemic vascular remodeling. The information may offer insights to develop treatments based upon the restorative strength of vascular remodeling after ischemia.