Vasculature Changes Early After Stroke Using One-Hour MCAo Mouse Model at 9.4T

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Introduction: Restoration of cerebral blood supply at the early stages of stroke is critical for salvaging brain tissues at risk, however the detailed microvascular changes, which occur during reperfusion, have not been fully characterized. We measured vascular transformation during the reperfusion phase of a transient ischemia model in mice using steady-state intravascular contrast agent techniques. Previous studies have shown that relative cerebral blood volume (rCBV) measured using ΔR_2 and ΔR_2*, the transverse relaxation rate changes before and after contrast agent administration, reflects total and micro-vascular CBV [1,2]. The goal of this study was to measure acute phase cerebral reperfusion through changes in total rCBV, microvscalur rCBV, and vessel size investigating whether microcirculatory restoration following reperfusion was characterized by a return to a normal hemodynamic state, or whether regions in and around the occluded zone restored flow via non-physiological means.

Material and Methods: C57BL mouse (n=6: ~25g) was used in this study. Prior to MRI experiments, mice were prepared with one-hour transient middle cerebral artery (MCA) occlusion as described previously [3]. Following reperfusion, each mouse was put into the MRI scanner (9.4T, Bruker Biospin) for MR imaging. We used a birdcage RF head coil (inner radius = 0.6cm) for data collection. Multi-slice multi- spin echo (MSME, TR/TE: 3000/[10,20,30,40,50,60,70,80 ms]), gradient echo (GE, TR/TE: 1000/[3, 5, 8, 10 ms]), and diffusion-weighted spin echo (TR/TE: 3000/30 ms, b-values: 0, 721,1623 s/mm^2) sequences were used for image acquisition. All images were acquired with a matrix size of 96x96, FOV of 1.5x1.5 cm, and slice thickness of 0.5mm with total 16 slices. After the baseline image collection, SPION was intravenously administrated via femoral vein. Maps of relative cerebral blood volume (rCBV: ΔR_2*) and microvascular volume (MVV: ΔR_2) were calculated based on the following equation: $\Delta R_2(\Delta R_2^*) = \frac{1}{TE}\left(\ln\left(SI_{pre}\right) - \ln\left(SI_{post}\right)\right)$, where SI_{pre} and SI_{post} are signal intensities before and after SPION injection. The ΔR_2* and ΔR_2 were calculated from SI collected using TE values at 30 ms and 3 ms for for MSME and GE acquisitions, respectively. Then, the voxelwise vessel size index (VSI = ΔR2*/ΔR2) was calculated. Apparent diffusion coefficient (ADC) maps were obtained by exponential fitting of the diffusion-weighted data. For regional analyses, the overall stroke region was first identified based on the ADC value (below the mean contralateral ADC minus 2 standard deviations (STD)). Thereafter, infarction core and peri-infarct areas were determined from rCBV (ΔR_2*) maps. The regions pertaining to ΔR_2* values below the mean contralesional ΔR_2* minus five STD was considered as core infarct region. Meanwhile, the infarct regions defined by ADC but having ΔR_2* values above the mean contralesional ΔR_2* minus five STD was considered as peri-infarct areas.

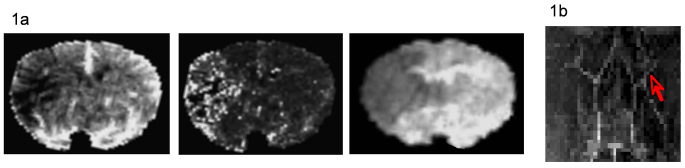

Figure 1: representative maps of rCBV (1a, left), VSI (1a, middle), and ADC (1a, right) showing the general infarction area and the heterogeneity of vascular response to stroke. 1b angiogram shows well reperfused MCA

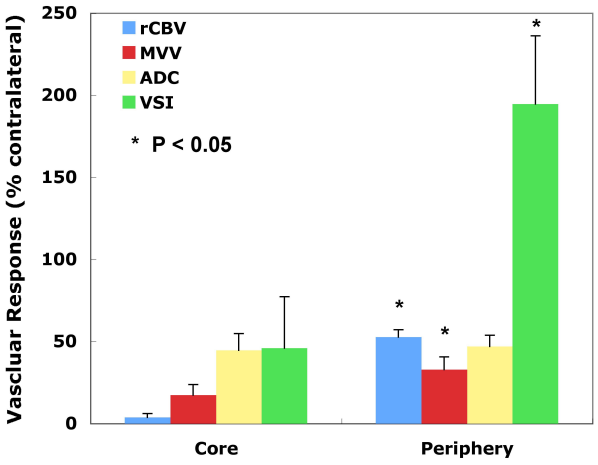

Figure 2: Vascular responses of total rCBV (rCBV), microvascular rCBV (MVV), vessel size index (VSI) and apparent diffusion coefficient (ADC) change four hours after reperfusion following one-hour MCAo in infarction core and periphery.

Results and Discussion: Fig 1a shows representative maps of rCBV, VSI, and ADC, in which heterogeneous spatial distributions of altered vascular and diffusion parameters were manifest in the ipsilesional hemisphere. Although the proper reperfusion of the feeding major artery (MCA) was indicated by MRI angiograms following the removal of filament (Fig. 1b), the ipsilesional rCBV measured from the infarct area did not fully recover to the normal baseline value (53 ± 4.5 % of that in contralesional side) (Fig.2). In general, rCBV, MVV, and VSI were significantly lower in the infarct core than those in the periphery as shown in figure 2. Interestingly, there was no apparent difference in ADC values between infarct core and periphery. The low rCBV, MVV, and VSI measured from infarct core indicate poor reperfusion, likely reflecting overall vascular collapse after 1 hr occlusion. In the infarct periphery, overall rCBV and MVV attained intermediate values between core and contralesional cortex, suggestion successful partial reperfusion. Surprisingly however, there was a pronounced increase in the VSI within these peripheral zones. The striking increase in vessel size index in the infarct periphery suggests that restoration of blood volume here is in part through larger vessels, suggesting extensive AV shunting. Our results suggest that at four hours after reperfusion following MCAo, the overall restoration of blood volume was spatially heterogeneous, and that the recovery of blood supply via microvasculature was small in both infarct core and periphery following the reperfusion. Perhaps more important, our data suggest that even where relatively effective, reperfusion in our mouse model was characterized by restoration of blood supply through non-physiologically functional (shunted) vascular units. This finding may have important implications for understanding effectiveness of reperfusion treatments in humans.

References: 1. Boxerman JL, et al MRM 1995 2. Dennie J, et al MRM 1998. 3. Atochin, DN et al, J Clin Invest. 2007

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