Cerebral blood flow autoregulation in transient ischemic tissue expressed delayed hyperperfusion two days after middle cerebral arterial occlusion

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Introduction: Strong hyperperfusion was observed in transient ischemic tissue 48-72 h after middle cerebral artery occlusion (MCAO) using the continuous arterial spin labeling (CASL) method [1,2]. Conversely, several reports have shown that CBF estimated by dynamic susceptibility contrast (DSC) does not show delayed hyperperfusion [3]. We have therefore performed CBF estimation using both CASL and DSC on the same rats whether a methodological artifact was existed. As delayed hyperperfusion was observed for both method[2], we have concluded delayed hyperperfusion should have a physiological basis. A possible physiological mechanism would be autoregulatory failure with full relaxation of resistance vessels. To confirm the physiological reason, we have performed sequential MRI observation and experiments for revealing cerebral blood flow (CBF) autoregulation with a lower body negative pressure method[4]. The lower body negative pressure method is useful to avoid an estimation error in CASL from a blood oxygen dependent signal change compared to traditional autoregulation experiment with hemorrhagic hypotension.

Methods: Eighteen male Sprague-Dawley rats (260-340 g) were used. Ischemic regions were induced by occluding the left middle cerebral artery with embolic thread under isoflurane anesthesia. After finishing occlusion, animals were allowed to awaken. Sixty minutes after occlusion, rats were re-anesthetized and the thread was withdrawn. Eleven rats were observed CBF, T_2-weighted image (T2WI) and isotropic diffusion –weighted image (DWI) in every 24, 48, 72 and 168h after reperfusion in 4.7-T MRI spectrometer (Unity Inova; Varian, USA). Seven rats were anesthetized again 48 after transient MCAO and brachial artery and vein were cannulated on the right hand for monitoring arterial blood pressure (MABP) and drugs administration. Then rats were set in the bore of the MRI spectrometer with a negative pressure chamber fitted for the lower half of the rat body (Figure 1). The acrylic chamber was connected to vacuum pump and an evacuation rate was automatically regulated by mass flow controller (Kofloc, Japan) for target value of MABP. For investigating the higher MABP, we administrated a phenylephrine (10 – 20 mg/kg/min). CASL was performed using a labeling neck coil (Rapid Biomedical, Germany). MRI for CASL was acquired using a gradient echo sequence with: response time (TR), 8 ms; echo time (TE), 4 ms; field of view (FOV), 25 mm; and matrix size, 64×64. Post delay of 400 ms was used for CASL CBF imaging. CASL CBF was calculated in accordance with previous reports [1,2,5].

Results: Figure 2 shows sequential MRI images in typical two transient MCAO model rats. Strong hyperperfusion in transient ischemic tissue was observed especially in 48 h after transient MCAO. Figure 3 shows the relationship between CBF and mean arterial blood pressure in seven rats. Open and fill rectangle show mean CBF of normal and ischemic caudate nucleus, respectively. Each point represents mean±SD of the blood flow in a 10 mmHg arterial pressure range. CBF in ischemic tissue is higher than normal tissue in all blood pressure range. CBF in ischmeic tissue remain constant in arterial pressure change between 100 and 150 mmHg. CBF autoregulation is still remain in normal tissue between 80 and 150 mmHg of MABP.

Discussion: We confirmed delayed hyperperfusion observed in CASL from sequential seven days experiment. CBF is much higher in 48h after transient MCAO, therefore we have investigated the autoregulation experiments at 48 h after transient MCAO. An autoregulatory failure was observed in the ischemic tissue. It should indicate the vessel dysfunction of shrinkage at normal blood pressure induce the delayed hyperperfusion.

References: [1] Wang et al., JCBFM 22; 253-261 (2002) [2] Nakamura et al., Proc IEEE EMBS 30, 839-842 (2008) [3] Li et al., Stroke 31; 946-954 (2000) [4]Herman et al., JCBFM, 26 ; 1189-1197 (2006) [5] Silva et al., MRM, 209-214 (1995)

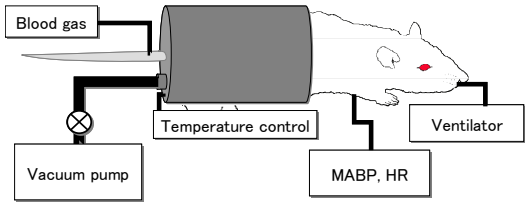

Figure 1

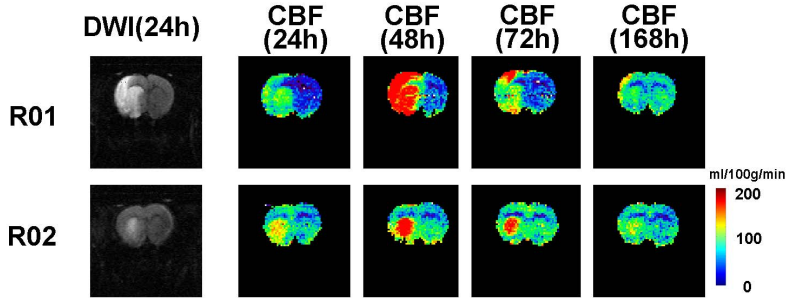

Figure 2

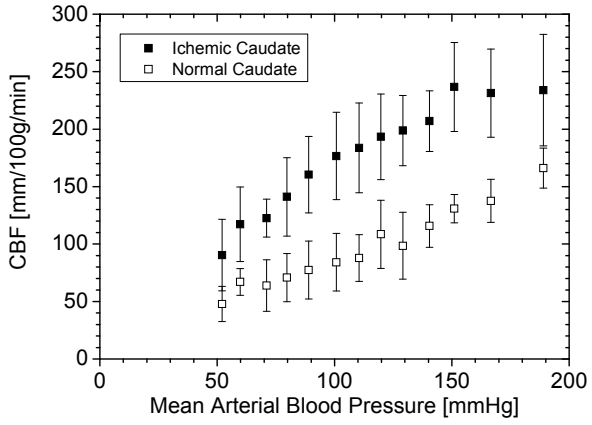

Figure 3