Quantitative evaluation of blood-brain barrier (BBB) permeability using Patlak Plots Methodology in a model of transient focal ischemia in rats

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Introduction

Studies have shown the power of dynamic contrast enhanced (DEC) MR imaging technique to spatially depict BBB opening occurring after ischemic infarct. One recent approach, the multiple time graphic method or Patlak plotting (1) provides an accurate method for estimating BBB permeability in reperfused ischemic infarcts (2). The previous results for identifying BBB disruption is limited to few time points only. The aim of this study was to evaluate the BBB-damage in a rat model of transient focal cerebral ischemia using the Patlak plot methodology at several time points up to 5 weeks. Quantitative MRI assessment of the ischemia induced BBB permeability changes was performed at 2,4, 6, 12, 18, 24, 36, 48, 72 hours and 7, 12, 21, 28 and 35 days after reperfusion. The K_j and V_p values via the Patlak plot approach were estimated for all imaging time points. In addition, other MRI parameters, ADC, and relative T2-weighted signal intensity (T2-ratio) were also measured to characterize the ischemic damage in this cerebral ischemia model. To our knowledge, such a study to detect BBB opening in reperfused ischemic infarct for long term follow up with MRI has not yet been reported.

Materials and methods

Adult male Wistar rats (n=100, 290 to 340 g), were anesthetized by an intraperitoneal injection of ketamin and a subcutaneous injection of medetomidine hydrochloride. Transient focal cerebral ischemia was induced by the intraluminal suture occlusion of the middle cerebral artery (MCA) for 90 min followed by reperfusion, as described elsewhere (3). Rats were positioned in the animal holder and transferred to the magnet bore (4.7 T Bruker Scanner) immediately after MCA occlusion and diffusion weighted images (DWI) sequence was run to confirm the presence of ischemia and calculate ADC values. The rats were then removed from the magnet and reperfused. They were divided into 14 groups, each with 6-8 rats, based on the time of Gd-DTPA injection after reperfusion. The rats were again transferred to the magnet after 2,4, 6, 12, 18, 24, 36, 48, 72 hours, and 7, 14, 21, 28, 35 days after reperfusion. DWI and T_1 measurements with an inversion recovery snapshot-FLASH (IR-FLASH) sequences were acquired, then a bolus of GD-DTPA (0.1 mmol/kg) was injected into the femoral vein (injection time < 5sec) after which repeated IR-FLASH sequence was run at ~ 1 min intervals for 20-30 min. A single slice was imaged in the region of the maximum enhancement according to DW and post T1weighted images.

Results

Figure 1 illustrates the characteristic MRI pattern (T2W, DW, T1W post Gd-DTPA injection, post T1 map) observed at several time points (2, 24, 48 hrs and 1 and 5 wks) after reperfusion. In all animals included in the study, within minutes after occlusion, DW images depicted ischemic injury. The time course of lesion evolution was observed both in DW and T2W images at several time points. BBB damage after reperfusion occurred on postcontrast T1-weighted images. The group mean for K_i and V_p for different groups are shown in Fig. 2 (a, b). The slopes of the lines for the Patlak plot (K_i values) of ischemia regions (cortex and subcortex) for all groups were statistically different than zero ($P < .01$) unlike those depicting the contralateral brain. The K_i values have a tendency to decrease linearly over time and reach minimum value at 3-5 weeks. There are high correlations between K_i and V_p.

Discussion

Our results show that BBB opening has occurred at all imaging times following 90 min of MCAO indicating a monophasic opening of BBB following ischemia-reperfusion injury. The results indicate that BBB opening once started, is an ongoing process (up to 5 wks), and is more severe at the beginning and the degree of severity decreasing slowly over time.

References

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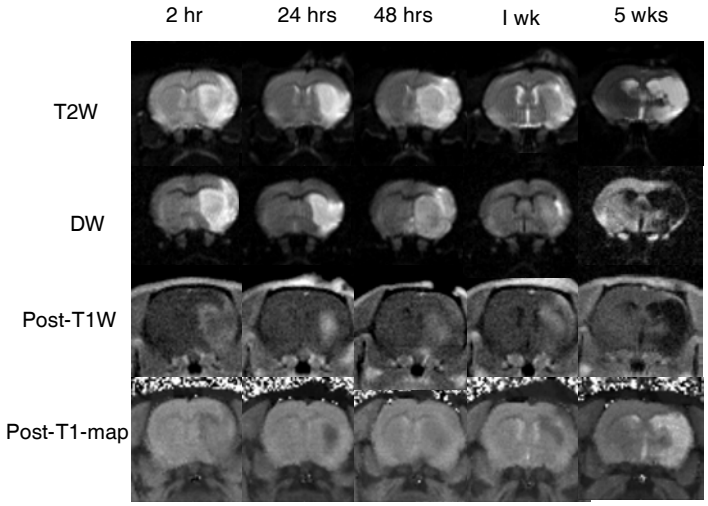

Fig. 1

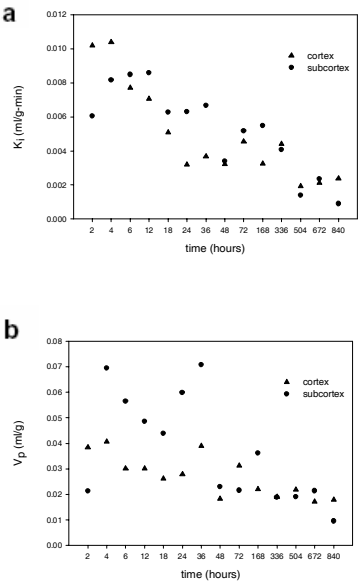

Fig. 2