Evolution of Diffusion Tensor Parameters of Ischemic Penumbra and Infarct Core in a Rat MCA Occlusion Model

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Introduction

Diffusion tensor imaging (DTI) has drawn much attention on clinical applications for its ability to measure three-dimensional water diffusion that delineates the micro-structural changes in the brain in cerebral ischemia [1]. In early cerebral ischemia, DTI parameters such as fractional anisotropy (FA) can be higher in ischemic region than that of contralateral normal brain, and then declines rapidly over the ensuing time course [2]. Contrary to the infarct core (IC) region, the ischemic penumbra (IP), which is often defined on MR images by lesion volume difference between perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI), is likely to benefit from reperfusion therapies [3]. It is plausible that these potentially viable cells in IP may exhibit different behaviors from cells in IC in regards to anisotropic diffusion. Therefore, the aim of this research is to measure the longitudinal evolution of FA in IP and IC regions using an animal model of ischemic stroke.

Materials and Methods

All MRI animal experiments were performed in a 7T scanner (PharmaScan 70/16; Bruker, Germany) with an active shielded gradient of 300 mT/m amplitude in a rise time of 80 μs. Middle carotid artery occlusion (MCAO) on a total of eight Sprague-Dawley rats rendered by permanent intra-luminal suture was applied. In addition, a PE-50 polyethylene tubing was inserted into the inferior vena cava via the left femoral vein for injecting the contrast agent Gd-DTPA (gadopentetate dimeglumine, Magnevist; Schering, Berlin, Germany) for PWI. Imaging was performed at 7 time points, starting at 0.5 hour after MCAO and followed every hour up to 6.5 hours after MCAO. Relative cerebral blood flow (rCBF) measurements were be made using the dynamic susceptibility contrast (DSC) MRI technique, where a series of 40 gradient-echo coronal slices with temporal resolution of 2 seconds were acquired. DTI acquired six non-collinear diffusion-weighted multi-shot echo-planar images (TR = 10000 ms, TE = 23 ms, NEX = 4) with navigator-echo correction and with b factors of 0 and 1100 s/mm2, which were subsequently used to calculate FA maps. The FOV for each pulse sequence was 25.6×25.6 mm, 1 mm slice thickness, matrix size = 64×64 and 18 slices of the same locations. All data were zero-filled to generate images with a matrix size of 128×128, and co-registered to allow region identification across images acquired from different sequences. IP was defined as regions showing rCBF < 62% ***but*** apparent diffusion coefficient (ADC) > 70% of the homologous tissue in the contralateral hemisphere [4]. IC was defined as regions showing rCBF < 62% ***and*** ADC < 70%. Moreover, ischemic lesion volume (ILV) was calculated by summation of IP/IC area, multiplied by the slices thickness, over the entire image volume.

Results

Figs. 1 and 2 showed the temporal evolutions of the spatial extents and percentage of IP and IC of ILV after MCAO, respectively. The IP volume was approximately 28% of the whole ILV at 0.5 hour (Fig. 2). As time evolved, the volume of IP decreased and eventually became IC. After 2.5 hours, IP and IC volumes accounted for about 15% and 85% of the whole ILV, respectively, and became stabilized (Fig. 2). Fig. 3 plotting the FA value as percentage changes relative to normal tissue revealed that the FA in the whole ILV was first elevated then decreased across time. When divided into IP and IC, a striking difference in time course of FA changes is seen (Fig. 4). IC showed continuous reductions in FA whereas changes in IP were relatively minor, but the difference decreased gradually. Notice that FA in IC (Fig. 4) seemed to dominate the trend of temporal evolution of FA in Fig. 3 due to larger percentage volume.

Discussion

Results from our study suggest that cellular swelling possibly begins within 0.5 hour after onset of ischemic stroke, which results in an average reduction of the extracellular space and a consequent reduction predominantly in transverse diffusivity [5]. The extent of this cellular swelling in IP does not seem to be as serious as in IC, hence leading to relatively unaltered FA values in IP within the 6.5 hours investigated in our study. In addition, the fact that the temporal evolution of FA in IP and IC merged at about 5 hours may have implications about the expected therapeutic window for the ischemic penumbra, i.e., 5 hours after stroke onset. In summary, findings from our MCAO animal may demonstrate reference value in patient management.

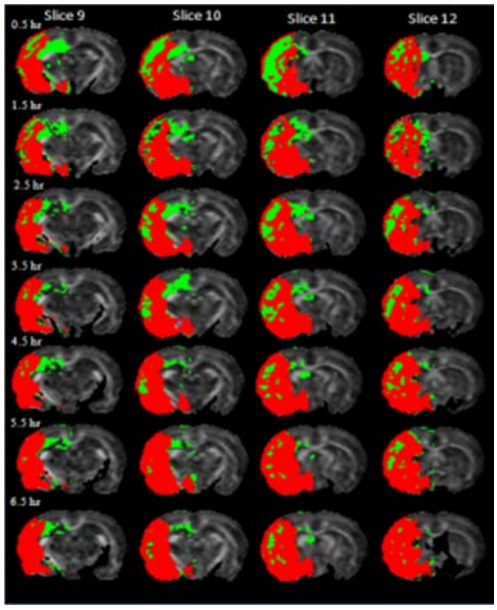

Fig. 1. Progression of spatial locations of IP (green) and IC (red) from one animal on FA maps.

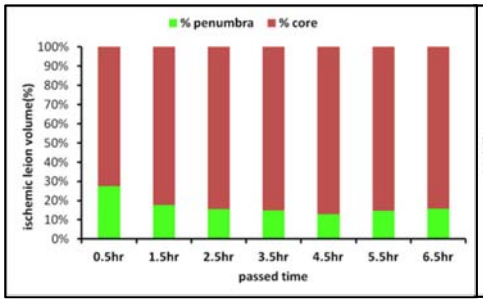

Fig. 2. Evolution of ILV. The vertical axis showed the percentage of IP (green)/IC (red) volume of the whole ILV. The volume of the IP remains average 15% of the whole ILV during permanent ischemia.

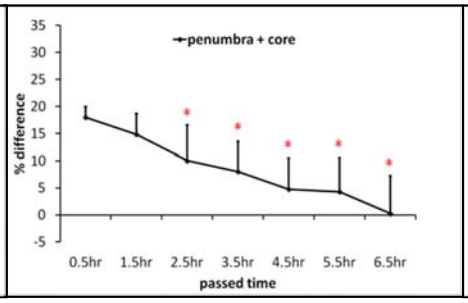

Fig. 3. Evolution of FA in the whole ILV (n=8). The difference values were calculated as follows: (FA_{lesion} - FA_{normal})/ FA_{normal}. A passed time labeled * indicates a significantly different ($p<0.05$) from 0.5 hr.

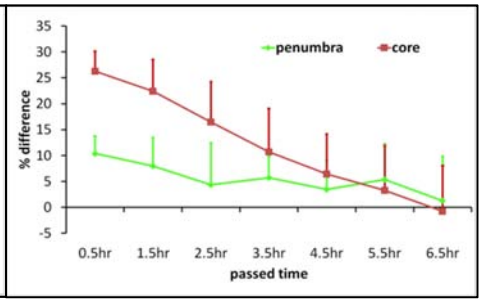

Fig. 4. Evolution of FA in IP (green) and IC (red), respectively. The mixed effects model showed a significant effect ($p<0.05$) in the time ×group on % difference of FA.

References

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