Investigation of Techniques to Quantify In Vivo Lesion Volume Based on Comparison of ADC maps with Histology in Focal Cerebral Ischemia Studies of Rats

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Introduction

Diffusion-weighted imaging (DWI) is effective in detecting the early stages of cerebral ischemia following the onset of stroke. Regions suffering a reduction in the apparent diffusion coefficient (ADC) of water highlight the ischemic lesion. Lesion volumes derived from ADC maps offer quantitative assessments of the extent and severity of injury, contributing vital information in exploring the efficacy of drug treatment or temporal evolution of ischemia. Previous studies have shown that lesion volume estimated from ADC maps compare well with histology (1-3). However, established criteria for applying these methods to stroke studies have been limited. The purpose of this study is to investigate different techniques for quantifying ischemic lesion volume based on comparison of ADC maps with histology in a rat middle cerebral artery occlusion (MCAO) model.

Methods

Lesion volume quantification techniques were tested on several data sets that were a part of three separate studies. In the first study, twenty-nine male Sprague-Dawley rats were subjected to permanent MCAO using a bithemiparal method. DWIs were acquired immediately after occlusion and at 30, 60, 90, 120, 150, and 180 mins following MCAO. In a second study, in-bore MCAO was performed on twenty rats following acquisition of three baseline data sets. DWIs were then acquired at 30 min intervals up to 180 mins following occlusion. The third study included three rats where ischemia was induced by an in-bore injection of microspheres into the carotid artery. DWIs were performed pre-occlusion and at 1, 2, 3, 24, and 48 hours post MCAO.

MR imaging experiments were performed with a GE CSI-II 2.01/35 cm imaging spectrometer (GE NMR Instruments, Fremont, CA) operating at 85.56 MHz for 'H and equipped with 220 G/cm self-shielding gradients. MRI data consisted of eight contiguous, axial 2-mm-thick slices, centered about the optic chiasm with field of view (FOV) = 25.6mm x 25.6mm and a 64x64 pixel resolution. Multislice, diffusion-weighted, spin-echo echo-planar imaging (EPI) was employed to map the ADC, on a pixel-by-pixel basis. Diffusion weighting was achieved by incrementing the gradient amplitude from 2 to 18 G/cm in 2 G/cm steps. Other parameters were TR = 5s, NEX = 2, s = 7, A = 35 ms. ADC maps were calculated from data acquired separately in the x-, y-, and z-gradient directions.

The lesion was excised at 72 hours post occlusion, sectioned into 2 mm slices, treated with TTC stain, and photographed by a CCD camera. Lesion was segmented from normal tissue using an image analysis program (Bio Scan OPTIMAS, Edmonds, WA) and lesion volume was calculated as percent hemispheric lesion volume (%HLV) using the method reported by Li et al (4).

An absolute ADC, threshold analysis was performed using in-house software on calculated ADC, maps obtained at the 180-min time point. Absolute ADC, threshold derived lesion volumes were compared to histological volumes (using a correlation plot) at multiple thresholds until the optimum value was achieved. The optimum absolute threshold was defined as that which yielded a linear trend line with a slope closest to one and a y-intercept closest to the origin.

A contralateral percent-reduction analysis for estimating lesion volume was performed. With software, each image was centered in the FOV and rotated to optimize contralateral comparisons. Additional software was employed to compensate for asymmetric brains and ensure that all pixels in the brain were evaluated. At the 180-min time point, pixels in the ischemic hemisphere were compared to homologous pixels equidistant from the midline in the contralateral hemisphere to calculate the percent ADC reduction. The optimal percent-reduction value was established as described above.

For studies using pre-occlusion baseline images, pixels in the ischemic hemisphere were compared to their original pre-occlusion ADC values to calculate the percent ADC reduction. In addition to comparisons with histology, pre-occlusion percent-reduction volumes were compared to contrast-enhancement volumes to investigate the assumption that contralateral ADC values effectively gauge pre-ischemic values for the ipsilateral hemisphere. Spatial correspondence was measured by calculating the ratio between the number of inconsistent lesion pixel locations of the two methods and the number of pixel locations where both methods found lesions.

Results

Optimal threshold values for the absolute ADC, and contralateral percent-reduction methods were evaluated in the permanent MCAO model. Lesion volumes derived from percent reduction values of 28%, 29%, 29.5%, 30%, 31% and 32% were plotted versus histological volumes. A percent-reduction value of 29.5% (shown in the figure) yielded the optimal slope (1.15) and y-intercept (-0.05). Lesion volumes defined by absolute ADC, values of 48, 49, 50 and 51x10^-6 mm^3/s were compared to histological volumes. The optimum absolute threshold was 50x10^-6 mm^3/s with a slope of 1.17 and y-intercept of 0.50 (not shown).

Discussion

Previous studies have demonstrated using absolute threshold to determine lesion volume in ADC maps because of anisotropy and the heterogeneity of intrinsic ADC values in brain tissues (5). However, Lythgoe et al. (6) showed that calculating the ADC, map mitigated anisotropic effects to a large extent. By experimentally choosing an absolute threshold for analysis on ADC, maps at a specific time point, this study has shown that lesion volume estimations with this method correlate and correspond well with histological volumes.

Percent-reduction analysis can provide further improvements over absolute threshold estimation of lesion volume. Comparing ADC, values in the ischemic hemisphere with those in the normal contralateral hemisphere removes potential errors in the absolute threshold analysis due to the heterogeneous nature of intrinsic ADC values in regions of the brain. The strong correlation between contralateral percent-reduction and pre-occlusion percent-reduction confirmed the effectiveness of the contralateral method for comparing homologous tissue regions. By accounting for brain asymmetry and by utilizing the ADC, in this study shows that contralateral percent-reduction estimates of lesion volumes at a specific time point correlate and correspond best with histological values.

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References

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