Characterization of MRI Lesion Development in a Macrosphere-Induced Embolic Stroke Model

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Introduction

The prevalence of stroke as a cause of death and disability has driven research to continually evaluate new animal models. The most widely used model for cerebral ischemia is the middle cerebral artery occlusion (MCAO) model, which can be achieved by MCA ligation or by introduction of an occluder. A microsphere-induced embolic model may exhibit more clinical relevance by providing variable, multifocal, and slow-developing lesions following injection of thousands of 0.005-0.02 mm spheres (1, 2). An alternative model involves the use of larger spheres (0.3-0.4 mm) for occlusion. Like the MCAO suture model, the macrospheres provide large lesions; however, this model does not induce hypothalamic ischemia, which can lead to larger lesion volumes due to neural interactions (3) and loss of temperature regulation (4). This study characterizes a macrosphere-induced embolic stroke model by examining the acute spatial and temporal development of ischemia using diffusion-, perfusion-, and T_2-weighted MRI.

Methods

Macrosphere-induced embolic stroke was studied in 11 male Sprague-Dawley rats. A PE20 tube was inserted from the ECA and placed in the carotid bifurcation. Six TiO_2 spheres (BRACE GmbH, Alzenau, Germany), 0.3-0.4 mm in diameter, were injected through the tubing. Eight animals received bench top macrosphere injection and histological preparation with TTC staining to determine the success rate of the model. Prior to slicing and staining, a standard microscope was used to determine the location of the macrospheres in the cerebral vascular. On three animals, diffusion-weighted images (DWI), perfusion-weighted images (PWI), and T_2-weighted images (T_2WI) were acquired at 0.5, 1, 1.5, 2, 3, and 4 hours post macrosphere injection. At 24 hours, the brains studied by MRI were excised, inspected under the microscope, and histologically examined.

MR imaging experiments were performed with a GE CSI II 2.0T/45 cm imaging spectrometer (GE NMR Instruments, Fremont, CA) operating at 85.56 MHz for ^{1}H and equipped with ±20 G/cm self-shielding gradients. All MRI data consisted of four (PWI) or eight (DWI, T_2WI) contiguous, coronal 2-mm-thick slices, centered about the optic chiasm with FOV = 25.6 mm × 25.6 mm and a 64 × 64 pixel resolution. Multislice, diffusion-weighted spin-echo echo-planar imaging (DW-EPI) was employed to estimate the trace diffusion on a pixel-by-pixel basis from three separate diffusion-weighted (x, y, and z) images. Diffusion weighting was achieved by incrementing the gradient amplitude from 2 to 18 G/cm in 2 G/cm steps. Other parameters were TR=5 s, NEX=2, δ=7, Δ=35 ms. T_2-weighted EPI was employed to perform dynamic contrast-enhanced perfusion imaging. A total of 40 images (TR=900 ms, NEX=1) was obtained for each slice. A bolus injection of 0.25 ml of gadopentetate dimeglumine was administered following acquisition of the fifteenth image. The relative cerebral blood volume (rCBV) and mean transit time (MTT) were determined for each pixel and used to calculated the cerebral blood flow index (CBF_i). A multislice, double spin-echo EPI pulse sequence was used to map the T_2 of the brain. T_2WI was achieved by varying the echo time for the first echo. T_2 maps were constructed from nine T_2-weighted EPIs with TR=5s, NEX=4, and TE_1 values between 20 and 110 ms. The echo time for the second echo was the same as the echo time for the DWI and PWI sequences (TE_2=74 ms). Using a linear least-squares regression, the natural logarithm of the signal intensity was fitted to the TE values, where the slope of the fitted line is proportional to the T_2 value.

On the calculated ADC maps, percent hemispheric lesion volumes (%HLV) were calculated from ADC maps using a comparison of pixels ipsilateral and contralateral to lesion with a percent reduction method using a threshold value of 33%.

Results

In the bench top validation study, six of eight animals demonstrated successful induction of stroke. The macrospheres lodged in different locations including the origin, trunk, and bifurcation of the MCA and in the Posterior Communicating Artery (PCoA), but none blocked the Hypothalamic Artery (HA). %HLV calculated from the TTC stained brains ranged from 20-55% with no infarction of the hypothalamus.

Figure 1 shows a representative DWI obtained at 4 hours post macrosphere injection. CBF_i maps indicated reduced blood flow in the region corresponding to the region of decreased ADC, however, T_2 maps did not detect the abnormality at this time point. In this example, the macrospheres blocked the origin of the MCA and the PCoA but not the HA producing a large lesion with no ischemia of the hypothalamus.

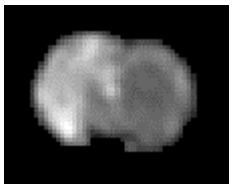

Figure 1. DWI of the ischemic rat brain at 4 hours following macrosphere injection.

Figure 2 shows the mean and standard error of the mean (SEM) of the ADC-derived %HLV change. At 4 hrs, the %HLV ranged from 41-57%, which matches the 42-60% hemispheric lesion volumes determined by histology.

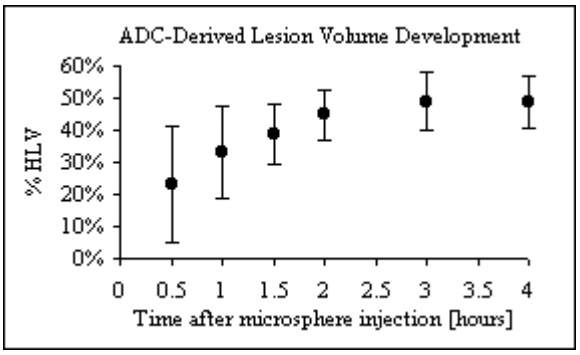

Figure 2. Mean and SEM of the %HLV as a function of time following macrosphere-induced embolic stroke (N=3). Like the MCAO model, the ADC-derived lesion volume at 3 and 4 hours corresponds to the %HLV measured by histology (51±9%).

Discussion

The macrosphere-induced embolic stroke model offers an alternative research model with the lesion size characteristics of the permanent MCAO model and the "clot" location variation of the microsphere model. Further, this model does not disturb blood flow to the hypothalamus, reducing the potentially confounding effects of neurological and temperature regulation enhancement of the lesion. Figure 2 indicates that the temporal evolution of this model is similar to the permanent MCAO model, where by the ADC-defined lesion is maximized by 3-4 hours post occlusion. However, the initial lesion volume of the macrosphere model is more variable possibly due to the uncontrolled macrosphere time-to-occlusion and location. This occlusion technique may provide additional clinical relevance to ischemia and treatment studies.

References

1. Zivin JA, DeGirolami U, Kochhar A, Lyden PD, Mazzarella V, Hemenway CC, Henry ME, *Brain Res* **435**:305-309 (1987).

2. Mayzel-Oreg O, Omae T, Kazemi M, Li F, Fisher M, Cohen Y, Sotak C, *Proc. ISMRM*, 1294 (2000).

3. He Z, Yamawaki T, Yang S, Day AL, Simpkins JW, Naritomi H, *Stroke* **30**:2743-51 (1999).

4. Li F, Omae T, Fisher M, *Stroke* **30**:2464-71 (1999).