Development and Evaluation of a Reversible Embolic Stroke Model for MR Endovascular Thrombolysis

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Synopsis

As part of our ongoing effort to develop MR-guided endovascular therapies, we are developing animal models of embolic stroke by injecting thrombus, via catheters, directly into the cranial circulation. Unlike glues and other embolic materials, our model is potentially reversible via thrombolysis. We have evaluated the technique in a series of six animals using x-ray angiography, MR imaging and colored microspheres. In particular, the use of intra-arterial (IA) contrast injections in MR perfusion-weighted imaging (PWI) has been evaluated. Here, we summarize our favorable early findings in developing and evaluating this model.

Introduction

Treatment of acute thrombo-embolic stroke requires immediate re-establishment of vessel patency. Thrombolysis using tissue plasminogen activator (tPA; Genetech, San Francisco, CA) is most commonly given intravenously; however in selected patients, direct IA thrombolysis has some advantages.[1] Motivated by these advantages and a longer (6 h) IA therapeutic window, we have begun to explore the benefits of detecting and monitoring ischemia, and delivering thrombolysis in MR. Here, we report our phase one findings: the development and evaluation of a reversible animal model of embolic stroke.

Methods

Autologous Emboli were prepared from 1 ml of arterial blood drawn from the animal and allowed to coagulate for >1 h, sectioned, and then passed through 0.5 or 1 mm mesh sieves. The prepared emboli were mixed with ~5 ml 0.9% saline and placed in a syringe.

Animal Preparation: Six animals (2 cats and 4 dogs) were used. Each animal was sedated and prepared in our animal facility (located adjacent to our MR scanner). Catheters were inserted via the femoral arteries under x-ray guidance (OEC 9800; General Electric Med Sys, Waukesha, WI). One catheter was placed into the left ventricle (for microspheres administration), and the other catheter was placed into the cranial arterial circulation (for emboli administration and IA contrast injections).[2] Initially, conventional catheters (4 French) were placed into the common carotid artery. In the last animal, a guide catheter/microcatheter (2.3 French) combination was placed into the internal carotid artery. Microspheres were injected in some animals, before and after embolus injection, to validate changes in perfusion.

MR Imaging was performed on a 3 T MR system (Signa; General Electric). We focused on understanding PWI methods using IA injections. The evaluated methods were: (M1) a 2D gradient-recalled echo technique (GRE: TR/TE = 10 ms/ 6 ms, 16 slices every 5.3 s), and (M2) a 2D single-shot GRE echo planar imaging technique (EPI: TR/TE = 1750 ms/ 45 ms, 12 slices per 1.8 s). The injection protocol consisted of (I1) injection of 1 ml of 50 mM contrast agent (Magnevist; Berlex, Wayne, NJ) over 3 s, followed by 5 ml of flush (via a conventional catheter); or (I2) injection of 12.5 mM contrast agent (5 ml over 5 s, via a microcatheter).

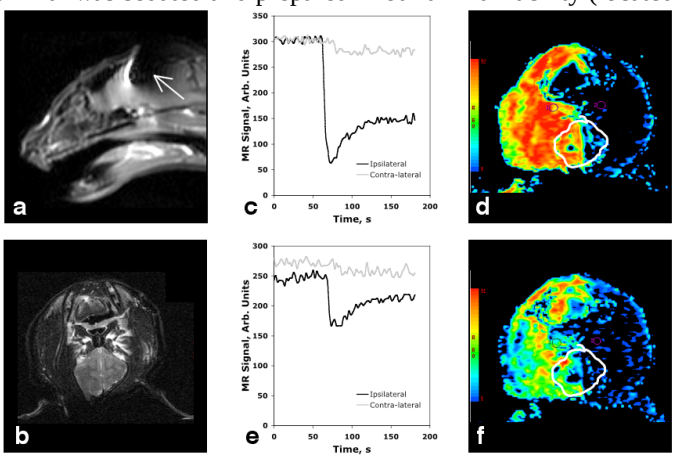

Figure 1: Cat experiment showing successful creation of a stroke using injection protocol I1 via the right carotid artery. Shown are (a) saggital localizer with microchip artifact (arrow), (b) axial T2-weighted image, (c,e) plots of MR signal versus time obtained with PWI method M1, and (d,f) plots of maximum fractional signal change. Signal change is much larger before injection of embolus (c,d) than after (e,f). White outline is brain.

Results and Discussion

The autologous emboli model succeeded in producing a stroke in all animals. X-ray imaging, MR PWI, and microspheres confirmed this result. Monitoring with PWI using both methods and injection protocols was successful (Figures). With the microspheres, difficulties were encountered in sampling the arterial blood, so only cerebral blood volume (CBV) measurements were available. These values indicated maximum reductions of about 60% in the affected territories. In a dog, IA tPA was administered and found to result in a temporary re-establishment of blood flow, however this change was not sustained (likely due to the large volume of injected emboli). Signal loss and distortion from implanted microchips (for animal identification) was found to be a problem (Figure 1a) in most experiments.

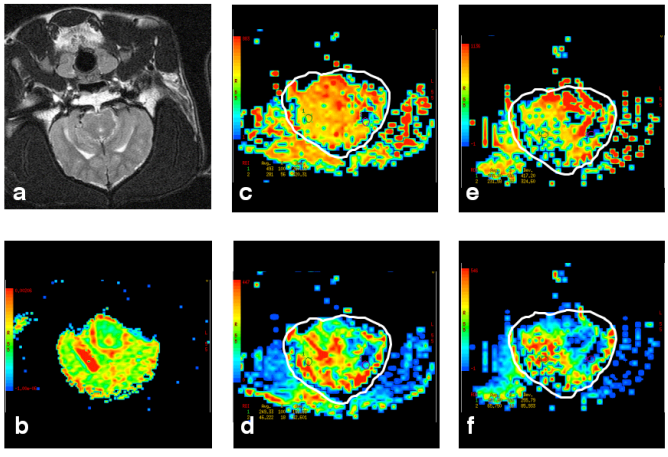

Figure 2: Dog experiment. Shown are (a) T2-weighted image, and (b) apparent diffusion coefficient, (c,e) relative mean transit time (rMTT), and (d,f) relative cerebral blood volume (rCBV) maps. Images were collected before (a,c,e) and after (b,d,f) injection of embolus via the left internal carotid artery. Note the increase in rMTT and the decrease in rCBV maps in the left hemisphere. PWI method was M2 and injection protocol was I2. White outline is brain.

Conclusions

Our preliminary evidence suggests that we are causing reversible emboli in animals. Microcatheters were required to prevent vessel occlusion by larger catheters. Future experiments will determine the volume of emboli to inject. We hope to use MR to detect and treat embolic stroke in animals as a prelude to human studies.

References

1. Zaidat OO, Suarez JI, *et al*. *Stroke* 2002; **337**: 1821-1827.
2. Frayne R, Omary RA, *et al*. *JCVIR* 2000; **11**: 1277-1284.