MRI of Emboli Localization and Lysis in an Embolic Model of Rat Middle Cerebral Artery Occlusion

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Introduction: The embolic model of rat middle cerebral artery occlusion is widely used for preclinical testing of neuroprotective drugs. While the time course of the perfusion and diffusion lesion have been described, little data has been collected to describe the time course of clot lysis during tissue plasminogen activator (tPA) administration in this model. To provide another level of characterization, MR imaging was performed during occlusion and throughout administration of tPA to understand the clot lysis dynamics and the resolution of the perfusion lesion.

Methods: All animal research was conducted with approval from the University's IACUC. Prior to imaging, blood was withdrawn from the tail artery and doped with Magnevist (Bayer, Wayne, NJ). The blood was processed to create standard clots as previously described [1]. In some animals, clots were stained with Evans Blue for histological localization. Middle cerebral artery occlusion (MCAO) in eight Wistar rats was induced by injecting the clot at the base of the skull. Following occlusion, rats were positioned on a 3cm actively decoupled head coil with a butterfly neck coil for Arterial Spin Labeling (ASL). All images were acquired on a Bruker 4.7T MRI using Paravision software. Baseline diffusion weighted images (DWI), ASL based perfusion weighted images (PWI), and MR angiography (MRA) were acquired. A set of centric ordered T1 weighted RARE images (T1WI) with a TR = 250ms, TE = 6ms and RARE factor = 4 were acquired in the area of the Circle of Willis for clot localization. Animals then received either tPA or vehicle infused over an hour and serial T1WI and PWI were acquired every 15mintues. Following drug administration, the initial baseline sequence was repeated. Following imaging, the brains were removed and the remaining clot was identified by its dark appearance in the vasculature.

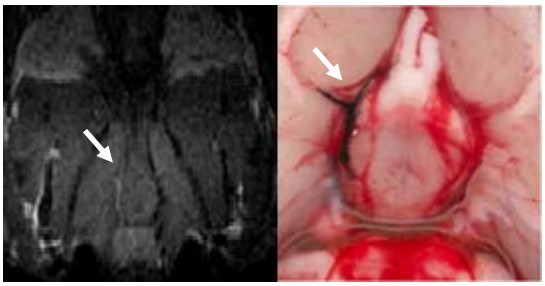

Figure 1: Clot localization on T1WI (left) and Evans Blue histology (right). Arrow points to areas of clot.

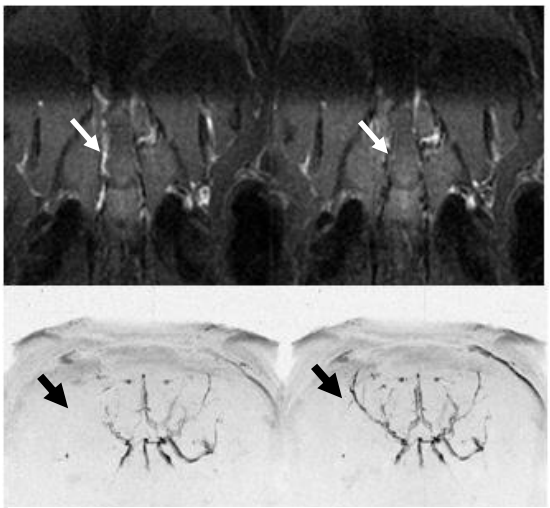

Figure 2 Clot visualization before (left) and after (right) tPA administration. White arrows points to areas of clot. The black arrows point to the location of MCA on MR angiography. The absence and reappearance of the MCA on MR Angiography confirm results.

Results: Figure 1shows an example of clot localization in a vehicle group. In this group, the structure and position of the clot remains steady over time. Evans Blue histology reveals similar clot localization as that shown on the T1WI. Figure 2 shows an example image of the clot before and after treatment with tPA. The clot is visible in the circle of Willis and in the Middle Cerebral Artery. Following treatment, the clot is no longer visible. This is confirmed with MR angiography (Figure 2). ASL perfusion imaging revealed a CBF drop over the duration of TPA from a starting value of 48±1% of the contralateral side to 16±1%

Discussion: To our knowledge, this work represents the first time clot lysis was directly observed in a rat model of embolic stroke. In both control and tPA animals, the initial clot localization as observed from T1WI is consistent with a lesion found on both DWI and PWI as well as with MRA. We have shown that the action of tPA serves to reduce both the signal intensity and length of the clot. Reduction in signal intensity can be attributed to a thinning of the clot due to the action of tPA. The technique presented here is not only useful in further characterization of the stroke model but may provide a means to test the efficacy of novel lytic compounds by characterizing the effectiveness of the lysis process.

Ref: [1] Henninger et al. J Cereb Blood Flow Metab. 2009 Jan;29(1):119-29