

Determination of optimal parameters for intra-arterial injection and blood brain barrier disruption in the mouse using MRI

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Introduction: Many promising therapies for neurological disorders fail due to the difficulty of achieving therapeutically relevant concentrations of the drugs in disease afflicted tissue. This is primarily due to the presence of the blood brain barrier (BBB), which is a physical barrier comprised of tight junctions between the vascular endothelial cells of the cerebral capillaries. The BBB prevents large, lipophobic molecules from passing from the blood stream to the brain, and as a result systemic delivery of large therapeutic constructs designed to treat neurological diseases is doomed to failure. One technique that may provide significant advantages for drug delivery is intra-arterial (IA) injection, where therapy is delivered into the artery or arteries supplying the disease afflicted area. This method is capable of achieving very high drug concentrations in the targeted tissue, with reduced systemic exposure and concomitant side effects. Although this delivery route does not bypass the BBB, it can be used for neural drug delivery if the BBB is permeabilized prior to injection^[1,2]. This can be accomplished, for example, by exposing the vessels of the brain to a hyperosmolar solution. This technique draws water from the cells of the vascular endothelium, dilating the tight intercellular junctions of the BBB, which allows material in the blood vessels to pass into brain tissue.

Methods: The goal of this work was to develop techniques that allow controlled and reproducible BBB disruption via IA delivery of mannitol in the mouse to enable future IA delivery of novel treatments of neurological disease. We surgically positioned custom built polyimide microcatheters (169 μ m outer diameter) in the internal carotid artery (ICA) of mice. Mice were moved to the bore of a small-animal MRI system (Biospec 70/30 USR, Bruker-Biospin) and injected intra-arterially with 750 μ l of Gd-DTPA (1:19 dilution of Magnevist[®], Bayer Healthcare Pharmaceuticals, in saline) at a flowrate of 800 μ l/min while monitoring the distributed volume and rate of tissue uptake/washout of the injected agent in real time using a FLASH gradient echo pulse sequence with TR = 25ms, TE = 3.8ms, FOV = 25mm \times 25mm, and a matrix = 192 \times 256. This was performed both with and without prior IA injection of a hyperosmolar mannitol solution (25 wt/v%) to locally disrupt the BBB. Three different mannitol injections were used: 500 μ l at 1000 μ l/min, n = 8; 750 μ l at 800 μ l/min, n = 5; and 750 μ l at 1000 μ l/min, n = 8.

Results: We found that the volume and flow rate of injected mannitol affected the degree of BBB disruption (observed as an increase above baseline in normalized time courses of signal intensity in a region of interest as shown in Figure 1). For a given mannitol flow rate, the degree of BBB disruption increased with increasing injection volume. More importantly, different territories of the brain exhibited different levels of BBB disruption related to the order in which the feeding arteries branch from the ICA (Figure 2), which may be relevant to therapeutic strategies that hope to deliver agents to the whole brain in a single injection.

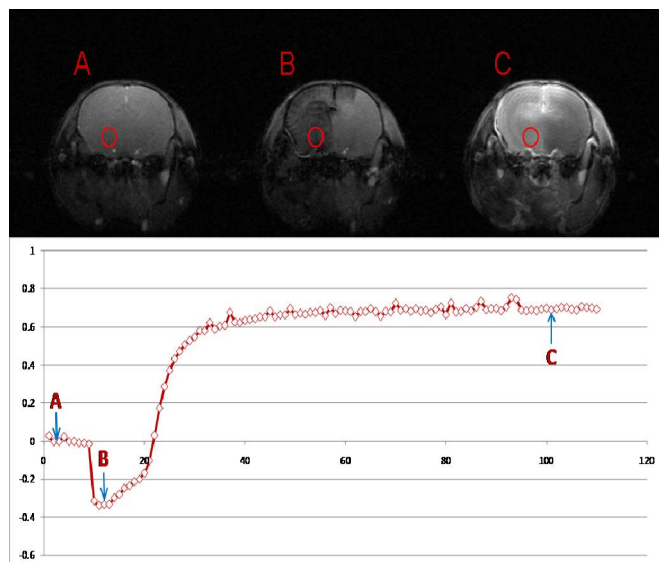


Figure 1. Representative time course of Gd-DTPA injection after BBB disruption, showing baseline image (A), 1st pass signal drop out (B), and steady state enhancement after contrast extravasation (C).

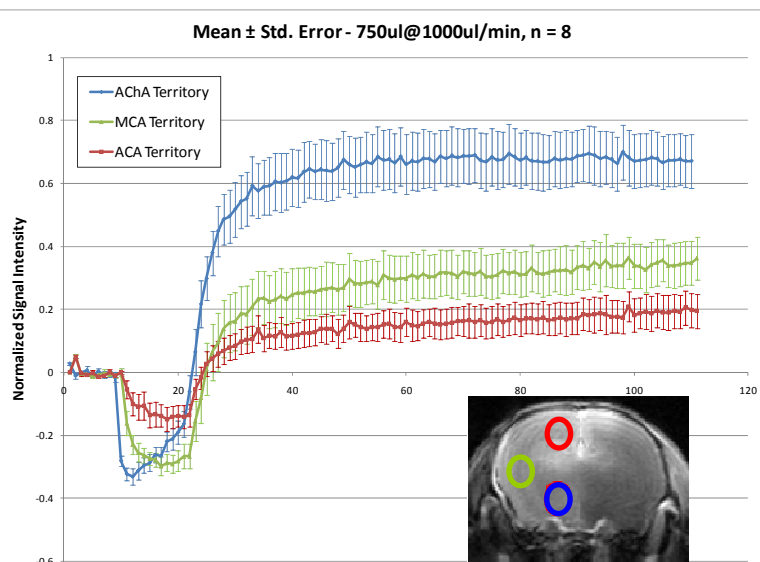


Figure 2. Mean signal intensity \pm standard error of the mean for three territories of mouse brain for Gd-DTPA injection after BBB disruption with mannitol (750 μ l at 1000 μ l/min, n = 8). Inset shows territories injected via the anterior choroidal artery (AChA, blue), the middle cerebral artery (MCA, green), and the anterior cerebral artery (ACA, red).

Discussion: The techniques demonstrated in this work enabled us to reproducibly disrupt the BBB in different territories of the mouse brain to varying degrees by changing the volume and flow rate of injection used. This should serve as a platform for future work on IA delivery in preclinical mouse models of human disease. Current work in our laboratory is focused on using USPIOs to determine the theoretical size cut-off of the osmolar BBB disruption obtained using these flow rates, volumes, and concentrations.

References: [1] – K.L. Black, *et al.* J Neurosurg, vol. 86, pp. 603–609, Apr 1997. [2] – N. D. Doolittle, *et al.* Cancer, vol. 88, pp. 637–647, Feb 2000.