Trans-catheter Perfusion MRI for Image-Guided Intraarterial Delivery of Therapeutic Agents to Target-Specific Brain Regions

Piotr Walczak[1,2], Miroslaw Janowski[1,2], Jeff WM Bulte[1,2], and Monica Pearl[3]

[1]*Radiology, Johns Hopkins University, Baltimore, MD, United States,* [2]*Institute for Cell Engineering, Johns Hopkins University, Baltimore, MD, United States,* [3]*Interventional Neuroradiology, Johns Hopkins University, Baltimore, MD, United States*

Target Audience: Physicians and scientists interested in specific, local delivery of therapeutic agents to the brain, including those working in the fields of stem cells, oncology, interventional neuroradiology, neurosurgery, and neurology,

Purpose: An intact blood brain barrier (BBB) represents a therapeutic challenge for the delivery of various agents to the central nervous system. Localized, intra-arterial (IA) BBB disruption (BBBD) provides an opportunity for enhanced delivery of therapeutics; however, the dynamic nature of cerebral blood flow contributes to variable efficacy. Perfusion imaging techniques allow for visualizing the precise territory of agent delivery. Endovascular procedures are performed under fluoroscopic guidance. The digital subtraction angiography (DSA) images opacify the intracranial vasculature and provide dynamic images of the arterial, capillary, and venous phases. The capillary or parenychmal phase is seen on DSA only with high perfusion rate of the contrast and effectively represents the entire area of brain supplied by the selected artery and may not reflect local delivery. The application of dynamic susceptibility contrast-enhanced MR-imaging using a clinically approved iron oxide MR contrast agent– Feraheme®- for precise, real-time monitoring of IA perfusion territory creates new therapeutic opportunities. The purpose of this study was to demonstrate in a rabbit model, the feasibility of MRI-navigated IA injection with local mannitol-induced BBBD.

Materials & Methods: 4-French sheaths were placed in the right femoral arteries of 4-kg New Zealand white rabbits (n=5). Via a transfemoral approach, the left vertebral artery was catheterized with a 4-French catheter. In a co-axial manner, a 1.7 French microcatheter was advanced through the guide catheter over a 0.014 inch microwire into the left V4 segment or basilar artery under roadmap guidance. Angiography was performed to confirm microcatheter position. All catheters were set to continuous heparinized saline flush. The rabbits were transported to a 3T Magnet (Magnetom Trio, Siemens) for dynamic imaging and intraarterial injections. Coronal T2 (TE/TR=105/1500), T1 (TE/TR=9.1/300), and GE-EPI (TE/TR=30/3000; 60 measurements) images were obtained prior to IA mannitol injection. Dynamic GE-EPI images were obtained during IA injection of saline diluted Feraheme® (0.3mgFe/ml). IA mannitol (25%, 50-100 µl/sec for 30 sec) was delivered at speeds corresponding to previous Feraheme® infusions. After 5 minutes, gadolinium (Magnevist 0.1 mmol/kg) and Evans Blue (EB, 2% w/v, 2 ml/kg) were injected i.v., and coronal T1 post-gadolinium images were acquired. The EB staining was evaluated post mortem on brain slices. In one animal, a focal disruption of the BBB was followed by IA infusion of iron oxide (Molday ION B)-labeled mesenchymal stem cells with their distribution detected by T2*w MRI.

Results: DSA facilitated a precise placement of IA catheters at the desired locations in the vertebral artery (**Fig. 1A**) or basilar artery (**Fig. 1D**). Dynamic GE-EPI depicted the perfusion territory following Feraheme® nanoparticle injection via the vertebral or basilar artery. Manipulation of the catheter tip placement and/or injection rate resulted in a differential brain parenchymal coverage (**Fig. 1B,D**). IA infusion of mannitol produced visible BBB disruption at the area previously demarcated by the Feraheme® perfusion imaging. The disruption was visible on gadolinium enhanced T1-weighted images as a focal enhancement within the medulla oblongata (**Fig. 1C**) or pons (**Fig. 1F**). Intraarterially injected stem cells distributed throughout the brain stem (**Fig. 1G**) and there was a marked preference for the cells to localize within the area with an opened BBB (white arrowheads; corresponding T1 image in **Fig. 1F**). Necropsy revealed unilateral Evans Blue uptake within the brain stem, which was notably smaller than the degree of T1 enhancement.

Conclusions: A transfemoral approach for microcatheter targeted IA delivery to the vertebro-basilar system in rabbits is feasible. We have shown that this approach is effective for producing local BBB disruption. This technique of targeting and BBB disruption may be exploited for highly specific and efficient delivery of stem cells, neuroprotective agents, gene therapy constructs or chemotherapeutic drugs.

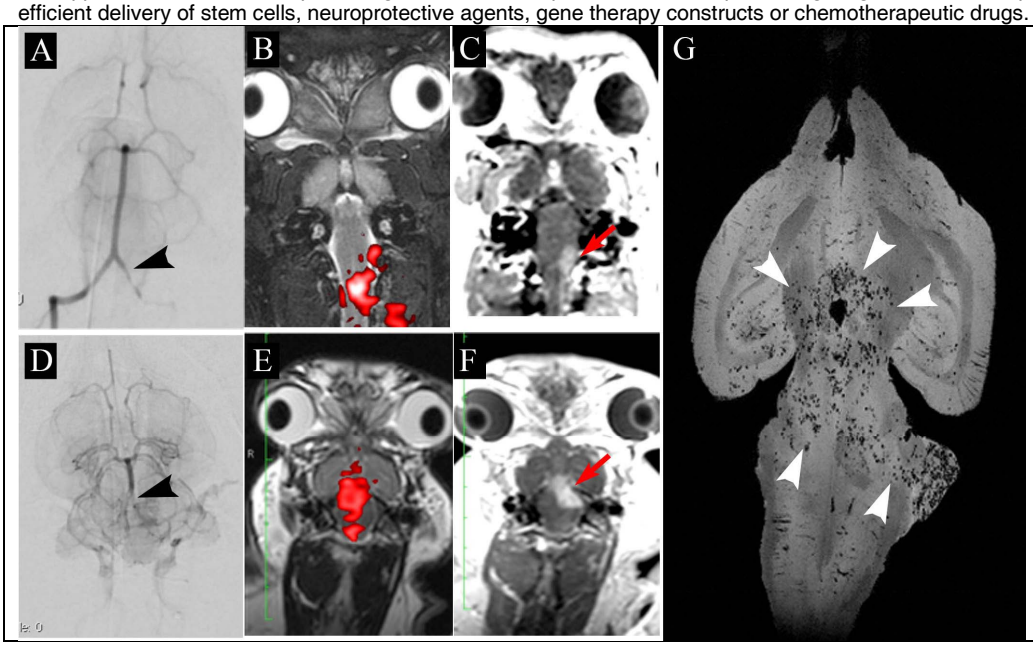

Figure 1. (**A-C**) Catheterization of vertebral artery. (**A**) DSA image showing microcatheter tip in the vertebral artery (black arrowhead). (**B**) Dynamic trans-catheter perfusion MRI with perfusion territory labeled in red and overlaid on T2 image. (**C**) T1w MRI showing disruption of the BBB in the area previously highlighted on the perfusion MRI.
(**D-G**) Catheterization of basilar artery.
(**D**) DSA showing microcatheter tip in the mid basilar artery (black arrowhead).
(**E**) Perfusion MRI showing a very different distribution compared to (**B**). (**F**) T1w MRI showing disruption of the BBB in the region corresponding well to the perfusion MRI. (**G**) T2*w MRI showing the biodistribution of IA-injected mesenchymal stem cells. Hypointense cells localize primarily in the brainstem (white arrowheads), in the area with disrupted BBB (seen in **F**).

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