

Dose Optimization for Combined Perfusion Weighed Imaging and Contrast Enhanced MRA using Gadofosveset

E. S. Poulsen¹, A. K. Olsen², D. Zeidler¹, N. Hjort¹, and L. Østergaard¹

¹Center of Functionally Integrative Neuroscience (CFIN), University of Aarhus, Aarhus, Denmark, ²PET-center, Aarhus University Hospital, Denmark

INTRODUCTION: Perfusion weighed imaging (PWI) provide crucial diagnostic and prognostic information in the diagnosis and treatment of patients presenting with symptoms of acute stroke. Current PWI protocols utilize standard Gd-based chelates with rapid vascular clearance to the extracellular fluid (ESF) space. While this property is ideally suited for subsequent visualization of tissue with severe Blood-Brain-Barrier (BBB) breakdown, it has been speculated that rapidly declining blood-tissue concentration gradients may preclude the detection of more subtle BBB leakage. In acute stroke, recent findings indeed suggest that early BBB leakage may herald subsequent hemorrhagic transformation¹. These findings remain inconsistent across studies, suggesting that BBB leakage sensitivity remain crucial to further explore the prognostic potential of this phenomenon¹. The use of contrast agents with long plasma half-life at high field for PWI and subsequent post contrast T1 weighted imaging is a particular promising strategy towards this goal. Meanwhile, prolonged blood-pool contrast allows steady-state Magnetic Resonance Angiography (sMRA), with high spatial resolution²⁻⁴. Gadofosveset trisodium (Vasovist®, Bayer Schering Pharma. Berlin, Germany) is a Gd-based contrast agent with high binding to serum albumin⁵. The prolonged plasma half-life allows the acquisition of steady state angiographies up to an hour after injection^{2,3,6}. While the use of gadofosveset for dynamic susceptibility contrast (DSC) MRI has not been reported in the literature, we hypothesize that contrast dosage can be optimized for PWI and subsequent sMRA. Here we simultaneously optimize gadofosveset dose to yield signal loss in T2* weighted DSC similar to that of a standard dose Gd-chelate and provide sufficient Contrast-to-Noise of cMRA in pigs.

METHODS: Six anesthetized female pigs weighing 40 kg were injected with a single dose of gadobutrol (Gadovist 1.0®, Bayer Schering Pharma. Berlin, Germany), followed by three gadofosveset trisodium injections of varying dosages [0.015-0.09 mmol/kg]. Scanning was conducted on a GE Signa HDx 3.0T imager (GE Medical Systems, Waukesha, USA). PWI sequence parameters were TR/TE 1500/30 ms, 60° flip angle, and sMRA performed with TR/TE 6,624/2,86 ms and 14° flip angle. Movement across serial examination were corrected by co-alignment and all images were then co-registered to an in-house landrace pig brain atlas. White and grey-matter VOIs were created from predefined atlas masks (frontal white matter and frontal cortex). T2* weighed images were analyzed for percent signal drop during peak bolus. T1 weighed images were analyzed for vessel versus white-matter contrast-noise-ratio (CNR). All experiments were approved and performed in accordance with the guidelines of the Danish National Committee for Animal Experiments.

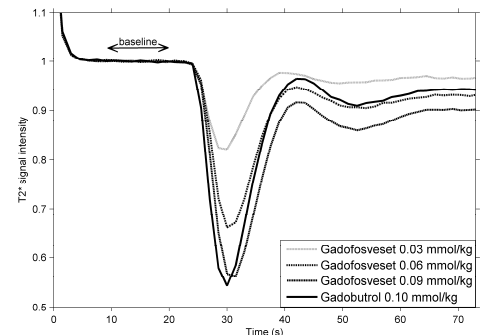


Figure 1. T2* signal intensity drop during bolus passage in pig no. 1. Three gadofosveset and standard gadobutrol dosages shown.

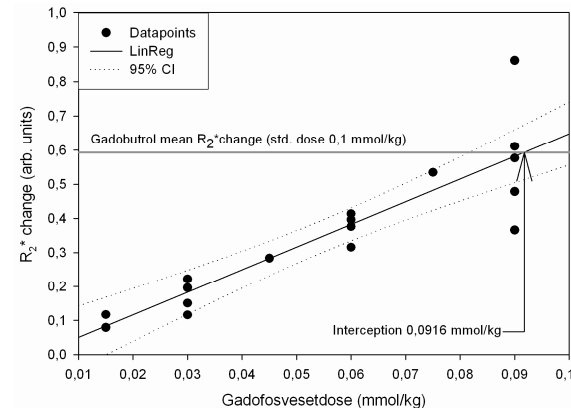


Figure 3. R2* change as a function of gadofosveset trisodium dose. Linear regression line shown. Dotted lines are 95% CI. Horizontal dashed line marks the average R2* change from six injections of a standard 0.1 mmol/kg gadobutrol dose.

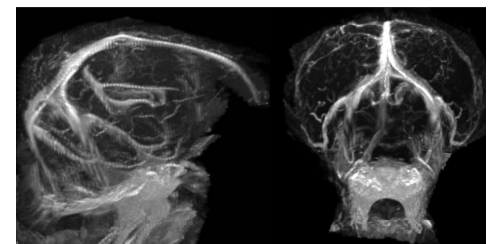


Figure 2. Examples of gadofosveset based sMRA of the pig brain.

T1 weighed images were analyzed for vessel versus white-matter contrast-noise-ratio (CNR). All experiments were approved and performed in accordance with the guidelines of the Danish National Committee for Animal Experiments.

RESULTS: A dose of 0.0916 mmol/kg gadofosveset trisodium was found to generate a T2* signal drop equivalent to that of 0.1 mmol/kg gadobutrol. At this dose, T1 CNR - dose relation was flat suggesting an optimal dose for sMRA. When adjusted for dose, mean DSC signal drop in grey matter was 30,8% greater than that of white matter.

DISCUSSION: We have demonstrated the feasibility of gadofosveset based PWI. The relaxation and plasma half-life properties allow detailed sMRA angiographies and may prove useful in detecting subtle BBB leakage of significance in e.g. acute stroke. Demonstration of the potential advantages of early identification of BBB disruption awaits clinical trials. We suggest a bolus dose of 0.0916 mmol/kg for acquiring PWIs equal to those generated with 0.01 mmol/kg gadobutrol.

REFERENCES:

1. Hjort N, Wu O, Ashkanian M, et al. MRI Detection of Early Blood-Brain Barrier Disruption. Parenchymal Enhancement Predicts Focal Hemorrhagic Transformation After Thrombolysis. *Stroke* 2008.
2. Bluemke DA, Stillman AE, Bis KG, et al. Carotid MR angiography: phase II study of safety and efficacy for MS-325. *Radiology* 2001;219(1):114-122.
3. Grist TM, Korosec FR, Peters DC, et al. Steady-state and dynamic MR angiography with MS-325: initial experience in humans. *Radiology* 1998;207(2):539-544.
4. Nikolaou K, Kramer H, Grosse C, et al. High-spatial-resolution multistation MR angiography with parallel imaging and blood pool contrast agent: initial experience. *Radiology* 2006;241(3):861-872.
5. Caravan P, Cloutier NJ, Greenfield MT, et al. The interaction of MS-325 with human serum albumin and its effect on proton relaxation rates. *J Am Chem Soc* 2002;124(12):3152-3162.
6. European Medicines A. Vasovist: Scientific discussion. 2008.