The Effects of Injection Rate on Vascular Signal Intensity Profile in a Porcine Model using Four Gadolinium Contrast Agents: Comparison Between Observation and Prediction Based on Measured Blood Relaxivity Values

Jeffrey H Maki[1], Guenther Schneider[2], Alexander Massmann[2], Matthias Leist[2], Diane Wagner-Jochem[2], and Gregory J Wilson[1]

[1]*Radiology, University of Washington, Seattle, WA, United States,* [2]*Radiology, University Hosptial of Saarland, Homburg, Germany*

Introduction It is understood that increased i.v. contrast bolus injection duration decreases artifacts such as blurring and ringing in Contrast-Enhanced MR Angiography (CE-MRA) due to decreased k-space modulation (1). It is also increasingly realized that decreasing Gd injection rate or diluting contrast (2) is beneficial, as the peak signal in doing so only suffers minimally due to the complex relationship between R1 and R2* and Gd concentration in blood (3). This study explores the relationship between Gd injection rate and resultant CE-MRA arterial signal and duration in a porcine animal model with the hypothesis that reduced injection rates do not significantly decrease CE-MRA amplitude, but instead lengthen the bolus and thereby decrease artifacts.

Methods Time resolved dynamic CE-MRA was performed on eight juvenile common German swine (53-63 kg) at 1.5T (Aera, Siemens) during the administration of 3 separate bolus injections (standard dose each) of one of four gadolinium agents; gadoteridol (ProHance, Bracco), gadobenate (MultiHance, Bracco), gadobutrol (Gadavist, Bayer), gadofosveset (Ablavar, Lantheus) - 2 animals each agent, 24 injections total. Boluses were made in random rate order (infusion rate (IR) - 1,2,3 ml/sec), separated by at least 15 min (30 min gadofosveset). Dynamic thick slice sagittal CE-MRA (TR 4.6 ms, TE 1.4 ms, α 30^0) was performed with a temporal resolution of 1.74 s in order to evaluate MR signal intensity (SI) vs. time (Fig. 1). During MR acquisition, blood was simultaneously sampled (2 s temporal resolution - 45 samples) from a 5 Fr. aortic sheath (abdominal aorta - Destination, Terumo) and sent for mass spectrometer analysis to obtain true blood gadolinium concentration (pending). Prior to and following the rapid dynamic CE-MRA, cardiac output (CO) was determined by Qflow.

From 1 animal, arterial blood was doped to blood concentrations from 0.5 - 18 mM with each contrast agent per the technique of Wilson et. al. (3). R1 was analyzed per this work to determine the non-linear relationship between [Gd] and R1 due to a) protein binding effects (gadobenate, gadofosveset) and b) the effects of fast erythrocyte water exchange; r2* was fit to a linear model for each agent. Based on this, expected SI vs. [Gd] for any CE-MRA sequence and agent can be calculated.

Analysis of the gadobenate and gadoteridol animals (n=4) has been completed thus far. Signal intensity for each injection (1, 2, 3 ml/s) in each animal was determined from ROI measurement (abd aorta - CVI42, Circle) and plotted vs. time. Predicted SI_{max} for each injection rate and animal was determined based on the derived blood R1 and R2* relationship and instantaneous cardiac output and compared to imaging SI_{max}. Duration of SI > 80% of SI_{max} (t_{80}) was determined for each injection rate.

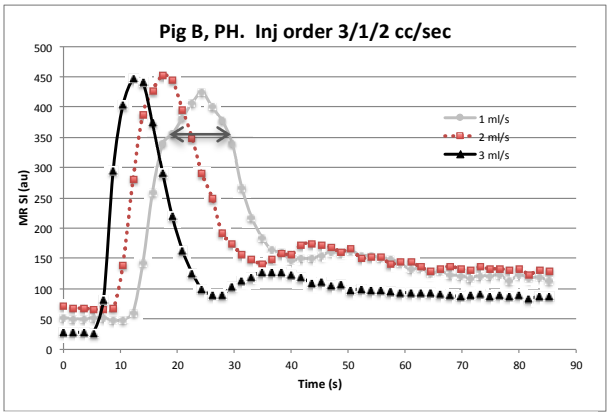

Figure 1. Example plots of SI vs. time post injection single dose gadoteridol. Note similar SI_{max} for each bolus rate but longer duration arterial enhancement for slower (=longer) injection. Double arrow represents t_{80} for 1ml/sec bolus.

Findings R1 and R2* relationships for Gd agents in porcine blood were quite similar to human (3), however R1 fit better using a shorter mean erythrocyte water residence time (5 ms vs. 10 ms), and r2* (at 1.5T) was somewhat greater than in human blood. This is fully reported in a separate abstract.

Despite predicted maximum [Gd] spanning nearly four-fold (6.6-27 mM - estimated as IR/CO), maximum observed SI for the different injection rates were only minimally different (Figs 1, 2). This was largely predicted based on the non-linear relationship between [Gd] and R1 and the deleterious effects of T2* as blood Gd concentration increases (Fig. 2).

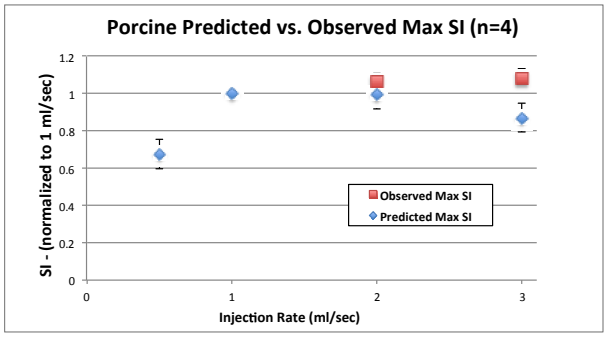

Figure 2. Mean relative Predicted vs. Observed SI_{max} *vs.* iv bolus rate for swine (n=4) injected with single dose gadobenate or gadoteridol. Note a quite "flat" response, with no increase in SI between 1 and 2 ml/sec (per prediction), and only slightly increased SI at 3 ml/sec (> prediction, see Discussion).

Injected gadobenate and gadoteridol volumes ranged from 11-13 ml/dose (0.1 mmol/kg) – thus i.v. bolus duration at 1 ml/sec was 11-13 sec; 1/2 or 1/3 this length for the 2 and 3 ml/sec boluses. The observed 80% maximum arterial time t_{80} vs. injection rate, as well as the ratio of t_{80} to i.v. bolus duration is shown in Table 1.

Inj Rate →	1 ml/sec	2 ml/sec	3 ml/sec
t_{80} (sec)	14.3 (1.7)	8.7 (1.4)	7.8 (1.7)
t_{80}/Inj Dur	1.22 (0.13)	1.48 (0.21)	1.98 (0.29)

Table 1. Average (std dev) duration of arterial enhancement > 80% maximum (t_{80}) per injection rate (middle row). Bottom row = ratio of arterial duration (t_{80}) to length of i.v. injection. Note the faster injections (2, 3 ml/sec) have much shorter peak durations (also see Fig. 1), much shorter than typical high-resolution CE-MRA which may be 15-20 sec.

Discussion The porcine model used is similar to human in size and cardiac output (~ 60 kg, ~ 5L/min). In addition, the relationship between [Gd] and R1, R2* in blood was determined to be very comparable to human, thus making it an excellent choice for testing the effects of different contrast injection strategies.

This study first and foremost demonstrates that SI does not significantly increase as injection rates increase beyond 1 ml/sec (Figs. 1, 2); attributable to a) decreasing R1 vs. [Gd] at high 1st pass Gd concentrations (2^o to erythrocyte trans-membrane water exchange) (3), and b) R2* effects in blood (somewhat less here at 1.5T than expected at 3T). Second, a slower injection (1 ml/sec) results in a 65% longer peak bolus SI (t_{80}) than does the same volume at 2 ml/sec (Table 1). This is important in terms of improving edge sharpness and CE-MRA quality, particularly considering the "typical" practice of full Gd dose at 2 ml/sec for CE-MRA. We further note that increasing the injection to 3 ml/sec does minimally increase SI (Fig. 2), even though theory suggests it should actually decrease SI (largely R2* effect). We believe this aberration is due to bolus hemodynamics, where the 3 ml/sec bolus duration is not of adequate duration to reach the "peak" 1st pass concentration = IR/CO. The mass spectrometer [Gd] measurements, when available, will help clarify this and allow determination of how accurately predictions of SI for CE-MRA can be made based on the modeled R1 and R2* values.

References

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3. Wilson GJ et al. Magn. Reson. Med. 2013. doi: 10.1002/mrm.25064.