Measuring glomerular protein leakage with dual-agent DCE-MRI: reproducibility in healthy pigs

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Introduction: Many renal diseases are associated with an increased albumin leakage across the glomerular membrane. However, since albumin is reabsorbed in the proximal tubuli, this is not always detectable in the urine samples. The aim of this study is to validate a dual-agent approach in DCE-MRI to measure albumin concentration directly in the proximal tubuli. DCE-MRI with the standard agent Gd-DTPA is used to determine GFR, and followed by a second injection of the protein-bound tracer Gd-BOPTA. The dependence of Gd-BOPTA relaxivity on protein concentration (1) leads to an underestimation of GFR (2), from which, in principle, tubular protein concentration can be determined using a calibration curve. Here we present first results on reproducibility and consistency of the measured values in healthy pigs.

Material and Methods: Four healthy 30 days old piglets (40kg) were examined in general anaesthesia (Ketamine/Propofol) in a 1.5T scanner (Magnetom AVANTO, Siemens Sector Healthcare). After anatomical sequences, DCE-MRI was performed with a saturation-recovery TurboFLASH sequence (1 axial and 2 coronal slices; temporal resolution 1s; TR 194ms; TE 0.96ms; IR 9ms; slice thickness 8mm). Half a dose (0.05 mmol/kg) of Gd-DTPA (Magnevist, Bayer Schering) was injected intravenously at 2 ml/s, and data were acquired for 10 min. Immediately afterwards, half a dose (0.05 mmol/kg) of Gd-BOPTA (Multihance, Bracco-Altana) was injected at the same rate, and measured for 10 min as well. Data were analysed off-line with the software PMI 0.4 (2). Tracer concentrations were approximated by relative signal enhancement S/S0-1 for both injections. An arterial input function (AIF) was extracted from a small circular ROI drawn inside the aorta on the axial plane. An image of the mean transit time (MTT) was calculated by model-free deconvolution of the Gd-DTPA data. Cortical ROIs were defined semi-automatically by setting a threshold on MTT, then manually excluding extra-renal pixels. ROI curves were fitted to the two-compartment filtration model (1), producing a measurement of tissue plasma flow and -volume, tubular flow (ie. GFR per unit of tissue volume) and the MTT of the tubular compartment. Statistical analysis was performed with paired t-tests.

Results: No albumin was detected in the urine of the pigs. Figure 1 shows typical ROI curves and model fits, for Gd-DTPA and Gd-BOPTA in the same subject. ROI data for all subjects are summarized in Table 1. Intra-individual comparison of plasma flow and -volume calculated with Gd-DTPA and Gd-BOPTA data did not show significant differences in any of the subjects, but tubular flow calculated with Gd-BOPTA was on average 36% lower than that calculated with Gd-DTPA ($p<0.01$). Interindividual variability of all parameters was small.

Plasma Flow ml/100ml/min	Gd-DTPA	172.1 ± 6.4
	Gd-BOPTA	188.7 ± 7.2
Plasma Volume ml/100ml	Gd-DTPA	15.3 ± 1.2
	Gd-BOPTA	13.7 ± 0.6
Tubular Flow ml/100ml/min	Gd-DTPA	19.6 ± 0.5
	Gd-BOPTA	12.2 ± 0.7

Table 1: Plasma flow calculated with Gd-DTPA and Gd-BOPTA did not show significant differences. Tubular flow calculated with Gd-BOPTA was significantly lower than with Gd-DTPA. Interindividual standard deviation was only minimal.

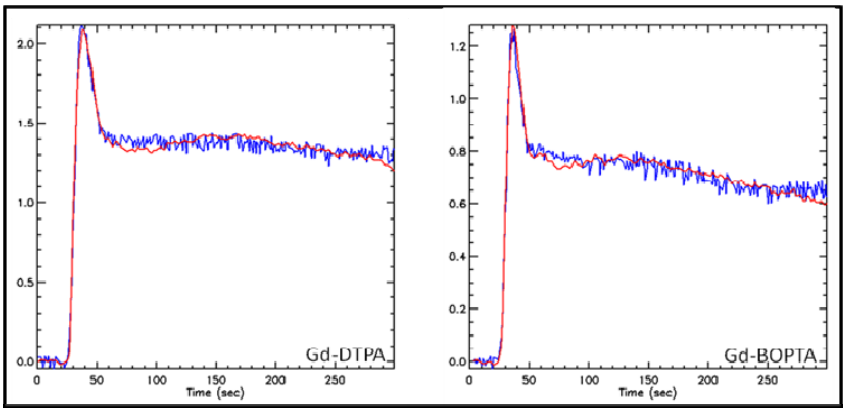

Figure 1: Cortical signal dynamics assessed with Gd-DTPA and Gd-BOPTA show distinct differences. The blue line is the measured data, the red line the fit provided by the model. Albumin binding of Gd-BOPTA leads to reduced apparent glomerular filtration in healthy pigs and faster declining signal intensity in the renal cortex in the excretory phase. Tubular flow calculated with the 2-compartment filtration model with Gd-DTPA was 20 ml/100ml/min, calculated with Gd-BOPTA 12 ml/100ml/min. Plasma parameters were

Conclusion: The agreement between plasma flow and -volume values obtained with Gd-DTPA and Gd-BOPTA provides strong evidence that the Gd-DTPA circulating at the time of Gd-BOPTA injection, does not cause significant systematic errors. The 36% understimation of GFR obtained from Gd-BOPTA agrees with expectations based on previous volunteer studies (1). The effect in pigs is somewhat weaker than in humans, which may be explained by a species dependence of the protein-bound Gd-BOPTA fraction. The small variability in the GFR values indicates that the measurement approach may be sufficiently precise to detect subtle variations in Gd-BOPTA relaxivity due to increased albumin leakage. This technique may help detecting such diseases in an early stage, where tubular reabsorption of albumin masks the leakage in urine samples. Further studies in a model with albumin leakage is warranted.

References:

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[2] S. Sourbron, et al. *Invest Radiol.* 2008; 43: 40--48.