In Vivo pH Imaging of Mouse Kidneys using Gd-DOTA-4AmP: Correcting for Susceptibility and Contrast Agent Compartmentation Artifacts

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Introduction. pH imaging of the kidneys by MRI has the potential to allow the non-invasive assessment of various diseases such as renal tubular acidosis. A technique to image renal pH in mice using sequential boluses of two contrast agents, the pH-insensitive Gd-DOTP and the pH-sensitive Gd-DOTA-4AmP, has been reported [1]. In this technique, the increases in apparent R_1 relaxation rate produced by each contrast agent molecule are used to compute pH on a pixel-by-pixel basis. Tissue structure and physiology can significantly alter the apparent *in vivo* relaxivity of a contrast agent. This is particularly true in the kidneys, which concentrate contrast agent molecules for excretion and separate water molecules into compartments with slow rates of exchange [2]. Concentrative accumulation of contrast agent molecules in regions of the kidney can introduce errors in pH computation by signal intensity loss resulting from significant T_2-shortening. High local concentrations of gadolinium will also exacerbate the artifacts produced by water molecule compartmentation [1, 3]. The uncertainty in calculated pH was found to be greatest in regions of the kidneys with the greatest gadolinium concentration – the calyces and renal pelvis. Theory indicates that the magnitude of these artifacts will depend on the T_1-weighting and T_2-weighting of the images collected dynamically after each bolus. Our objective in this work is to characterize these errors and devise an empirical strategy to correct for them.

Methods. MRI was performed on a Bruker Biospec 4.7 T system with 14 G/cm self-shielded gradients, using a 25 mm Helmholtz coil. Mice were anesthetized by inhaled isoflurane (1.5%, rest O_2 at 1 L/min), and circulating warm water jackets were used to keep animals warm in the magnet. Mouse body temperature was monitored during all MRI experiments using a rectal fluoroptic temperature probe (Luxtron Corporation, Santa Clara, CA, USA). Mice were cannulated at the tail vein prior to positioning in the magnet, and contrast agent (0.05 mmole/Kg) was administered via this catheter at the appropriate time during each experiment. T_1 maps or proton-density images were obtained in all cases prior to administration of contrast agent. The contrast-enhanced portion of each imaging experiment consisted of two consecutive phases: fat-suppressed spin-echo images were acquired every 6.5-30 s for 1 hour each following the injection of first Gd-DOTP, and then Gd-DOTA-4AmP. The following imaging parameters were used: in-plane spatial resolution = 273 μm, slice-thickness = 1-1.3 mm, number of slices = 1-3, recycle time (variable) = 50-300 ms, echo time (variable) = 6-30 ms. The renal pharmacokinetics of the pH-insensitive GdDOTP have previously been shown to be a good surrogate for the renal pharmacokinetics of the pH-sensitive GdDOTA-4AmP [1]. pH was calculated for each pixel from the pharmacokinetics of these two molecules and the pH-dependent relaxivity of GdDOTA-4AmP (measured *in vitro*). T_1-weighted spin-echo images with three different echo times (TE) were interleaved during acquisition, and a pH calculated for each pixel from the three interleaved data sets. In separate experiments, T_1-weighted spin-echo images with three different recycle times (TR) were interleaved during acquisition, and a pH calculated for each pixel from the three interleaved data sets.

Results. Our model predicts that water molecule compartmentation will not have a significant effect on the calculated pH in pixels with T_1 significantly greater than the TR. This assumption can fail in regions with very high contrast agent concentration. We have attempted to correct for this source of error by dynamically interleaving images with TR = 50, 100 and 200 ms, and extrapolating these data to compute a pH map at 'zero TR'. The dependence on TR of the error in the calculated pH was low in cortical pixels and significant in the renal pelvis. A corrected pH map is shown in figure 1. Experiments are also underway to characterize the errors arising from T_2-shortening in regions of high gadolinium concentration. In these experiments, pH maps will be computed from interleaved images acquired with varying TE, and correction will be attempted by extrapolation to 'zero TE'.

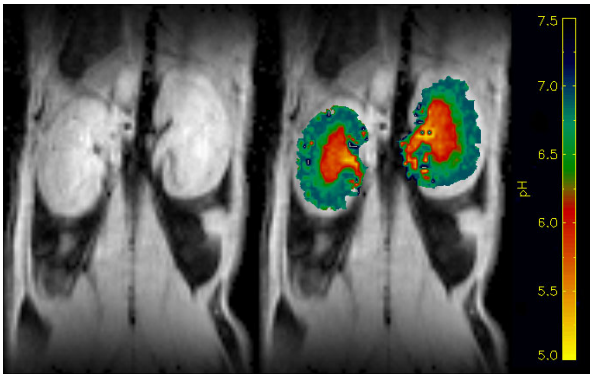

Figure 1. Left: Proton-density spin-echo image showing the kidneys in a mouse; Right: with superimposed calculated pH image of the kidneys showing pH 5.3-6.1 in the renal pelvis, pH 6.5-7.0 in the medulla, and pH 7.0-7.5 in the cortex. A pH of 5.9 was measured in a urine sample collected from this mouse immediately following the MRI experiment.

Conclusions. A dual-contrast-agent method has been employed to image renal pH in mice. The relationship between the calculated pH in a given pixel and imaging parameters (TR, TE, contrast agent dose) is being investigated. An empirical solution for correction of errors arising from T_2-shortening and water proton compartmentation is being developed.

References:

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