Phase-based Contrast Agent Concentration Measurement for Determination of Mouse Arterial Input Function

R. Yang[1], A. C. Yung[1], and P. Kozlowski[1]
[1]UBC MRI Research Centre, Vancouver, British Columbia, Canada

Introduction: Dynamic Contrast Enhanced (DCE) MRI and pharmacokinetic modeling have shown promise for imaging tumours based on tissue vascularity [1]. The volume transfer function between the plasma and interstitial space, K^{trans}, can be determined based on measurements of contrast agent concentration time-courses in these spaces [2]. The results of DCE-MRI are believed to have clinical significance for diagnosing tumours, as well as having value for investigating potential therapies in rodent models of cancer. The current standard method for measuring concentration relies on the linear relationship between contrast agent concentration and the changes in relaxation rate R1 (the reciprocal of T1) of water resulting from the presence of the contrast agent. However, this method is prone to inaccuracy, particularly in measuring the arterial plasma concentration time-course (called the arterial input function, AIF) [3]. T1-based AIF measurements in preclinical rodent tumour models have been reported in the heart [4] and tail vessel [5]. We propose an alternative method for obtaining the AIF in the mouse by performing phase measurements in the artery of the mouse tail. The magnetic susceptibility of the contrast agent introduces additional magnetic fields in the sample, which produce a change in signal phase within the vessel. We present experimental results, from a tail phantom, that demonstrate the feasibility of this technique.

Methods: A tail phantom was imaged in a 7T MRI scanner (Bruker, Germany), using a quadrature birdcage for transmission and a rectangular 1.5x1.5 cm surface coil for reception. The phantom consisted of a glass capillary tube (inner diameter: 0.4mm: outer diameter of 0.7 mm) placed in a larger tube (inner diameter: 3.7 mm; outer diameter: 4.6 mm) filled with water (Fig. 1). The length of the phantom was 6 cm. The capillary tube, simulating an artery, was connected to a KD Scientific Syringe Pump (KD Scientfic, Holliston, MA, USA), allowing for solutions to be flowed through the phantom at constant velocity. Ten solutions with different concentrations of gadodiamide (also known as Omniscan; GE Healthcare, USA) were flowed separately into the phantom at a speed of 8 cm/s that is similar to the *in vivo* situation [4]. A flow compensated FLASH sequence was used to image the phantom (TE = 6.154 ms, TR = 150 ms, FOV = 15 x 15 mm, 256x256 matrix, slice thickness = 2 mm, flip angle = 30°, BW = 200 kHz). The average phase change in the ROI (~35 pixels) encompassing the glass capillary tube lumen was calculated by subtracting the phase in the reference image (flowing 0mM solution) from the phase of the flowing contrast agent solutions using Matlab (Mathworks, Natick, MA, USA). The frequency shift per contrast agent concentration was found by dividing the phase shift per contrast agent concentration by the echo time. To test that the flow compensation FLASH sequence was working, the phantom with 0mM solution flowing through was imaged using the flow-compensation FLASH sequence and a normal FLASH sequence (both had TE = 6.154 ms, TR = 150 ms, FOV = 40 x 15 mm, 256x256 matrix, slice thickness = 0.32 mm, flip angle = 30°)

Results: A linear relationship was found between the phase change of the MRI signal and the concentrations of the contrast agent (Fig. 2). The slope of the fit was 0.41674π radians/mM gadodiamide and the intercept was 0.03149π radians. The amount of frequency shift per concentration of contrast agent in this geometry was then 33.9Hz/mM gadodiamide. Thus, to find the concentration for a sample, given the phase, simply divide the phase by (33. 9 Hz/mM gadodiamide*echo time). The flow-compensation sequence was shown to be successful in removing any phase accumulation from the flow (Fig. 3).

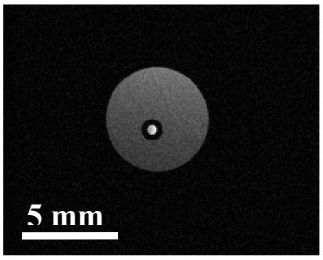

Fig. 1 Magnitude image of tail phantom with 8cm/s flow of 0 mM solution in capillary tube. TE = 6.154 ms, TR = 150 ms

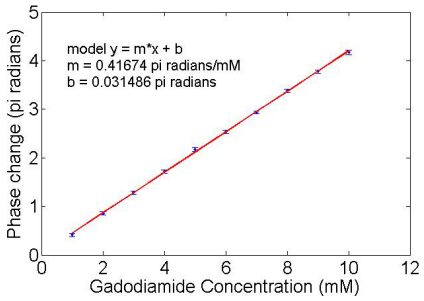

Fig. 2 Phase of capillary tube in relation to contrast agent concentration in tail phantom. 8cm/s flow solution was use in vessels of the phantom. TE = 6.154 ms, TR = 150 ms

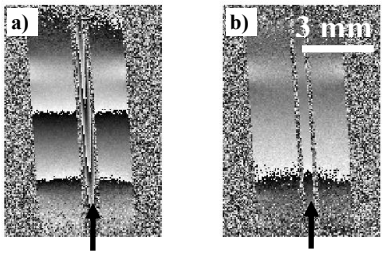

Fig. 3 Phase map of tail phantom (coronal view) with 0mM solution flowing at 8cm/s in vessel (arrow). TE = 6.154 ms, TR = 150 ms. a) no flow compensation b) with flow compensation. Note how the vessel and the rest of the phantom have same phase in b)

Discussion and Conclusions: McIntyre *et al* [5] has previously reported AIF measurement in the rat tail; however, these concentration estimates are prone to error due to nonlinear water exchange effects at high concentrations, as well as bias in flip angle and baseline T1 measurements. Our approach avoids these problems by measuring phase in the tail artery. In our phantom experiment, the phase increases linearly with gadodiamide concentration. The linear relationship between phase and concentration is not surprising, since local field inhomogeneities, which scale linearly with contrast agent concentration, cause the phase shift in the MRI signal. It should be noted that the phase shift, will depend on the geometry of the vessel. For example, Rochefort [7] used the phase measurements to estimate contrast agent concentration in the human aorta, but required a complicated numerical model of the geometry to derive the relationship between concentration and phase. Our approach has the advantage of having a calibration phantom that has good correspondence with the tail artery *in vivo*. The mouse tail can be modeled as an infinite cylinder, where the magnetic field disturbance is solely dependent on the susceptibility of the contrast agent and orientation with respect to the main magnetic field [8]. This work therefore presents initial groundwork for a method to measure the AIF in rodent models of cancer which is insensitive to the errors in T1-based measurements of concentration and is characterized by a straightforward calibration between phase and concentration,

Acknowledgments: This work was supported by a grant from the Natural Sciences and Engineering Council of Canada.

References: [1] Barentsz, et al. *J Magn Reson Imaging*,1999, **10**, 295; [2] Tofts, et al. *J Magn Reson Imaging*, 2009, **10**, 223; [3] Donahue, et. Al *J Magn Reson Imaging*, 1997 **7** 102; [4] Pickup ,et al, *Acad Radiol* 2003, **10**, 963; [5] McIntyre, et al, *NMR Biomed* 2004, **17**,132; [6] Reddy, et. al, Ultrasound Med Biol. 2003, **3**, 379; [7] Rochefort, et al. *Med. Phys.* 2008, **35**, 5328 [8] Chu, et al, *MRM* 1990 **13**, 239