Compartmental modelling of regional tumour glucose pharmacokinetics with quantitative glucoseCEST

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Introduction

GlucoseCEST utilises the exchange of protons in glucose hydroxyl groups with bulk tissue water protons to induce MR image contrast. By injecting unlabelled glucose, we showed that its uptake could be detected in tumor xenograft models [1,2]. We have recently proposed an extension to this method that enables glucose concentration to be quantified *in vivo*, using an empirically defined calibration [3]. Here, we evaluate the ability of this technique to quantify glucose pharmacokinetics via compartmental modelling of glucose enhancement curves in a tumour xenograft model of colorectal cancer, a technique we have named dynamic glucose-enhanced (DGE) MRI, and which is directly analogous to that used with gadolinium chelate-based contrast agents.

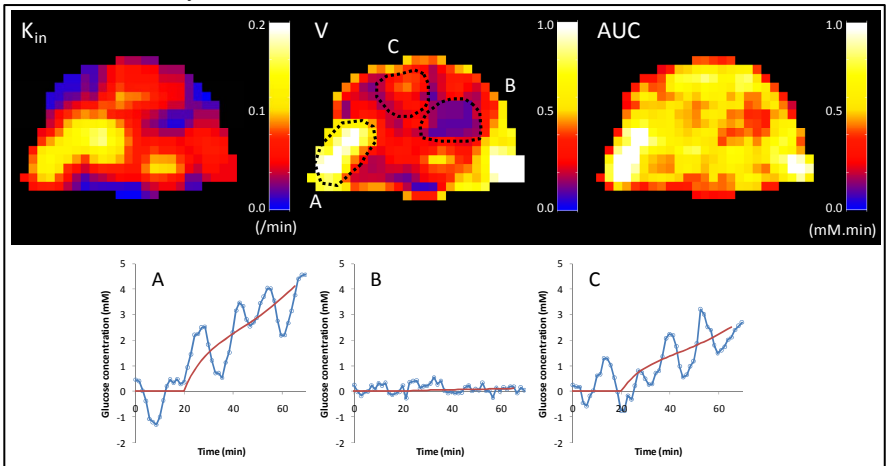

Figure 1. Top: Pharmacokinetic maps from fits to dynamic glucose-enhanced CEST data. K_{in} is the rate of wash-in of glucose, V is the volume accessible to glucose and AUC is the area under the curve. Bottom: The AIF used in the two-compartment model (from direct glucose sampling from a vein following i.p. injection) and average raw data and fitted curves from the regions of interest defined in the V parameter map above.

Methods and Materials

Tumor models: Subcutaneous tumors were propagated in nude CD1 mice by injecting 5×10^6 human colorectal carcinoma cells (SW1222) under the skin of the right flank, and were allowed to grow for 14 days. Prior to MRI scanning, mice were fasted for 24 hours in order to stabilize baseline blood glucose. Anaesthesia was induced using isoflurane (1.25% in O_2) and a non-metallic intraperitoneal (i.p.) line was inserted, primed with glucose solution (140mM in saline). Mice were positioned in the centre of a 9.4T Agilent VNMRS scanner and their temperature was monitored and maintained at 37°C using a warm air blower (SA Instruments). Dental paste was used to restrain tumors and avoid image artefacts caused by bulk respiratory motion.

MRI scanning: Tumors were localised using a fast spin-echo (FSE) sequence and whole-tumor shimming was performed using an automated sequence (ge3dshim) to give a typical water linewidth of 30 Hz. A baseline set of glucoseCEST data were acquired using a gradient echo imaging sequence (TR=6.1ms, TE=2ms, flip=5°, FOV=30×30mm^2, slice thickness 1mm, matrix size=128×128) with a train of three Gaussian preparation pulses prior to the acquisition of each line of k-space. Saturation pulses were applied at 101 frequency offsets covering ±6 ppm to encompass glucose saturation peaks between 1 and 3 ppm from water. A reference offset at 80,000Hz was also acquired for normalization.

Following the baseline scan, a dynamic glucoseCEST acquisition was initiated. This consisted of multiple repetitions of the baseline scan, but with frequency offsets at just 0, 1, 2, 3, 4 and 5 ppm in order to reduce scanning time (and thereby increase temporal resolution). The total scan duration was 70 minutes and temporal resolution was 1.4 minutes. At 7 minutes following initiation of the dynamic sequence, 0.2 g/kg of glucose solution was injected.

Post-processing: Baseline glucoseCEST data were converted to MTR_{asym} curves on a pixel-by-pixel basis by fitting a polynomial function to z-spectra, correcting for off-resonance effects by cubic spline interpolation and subtracting signal intensities at either side of the direct water saturation peak [4]. This procedure was applied to sparse dynamic z-spectra by constructing complete dynamic z-spectra from baseline data at -5, -4, -3, -2 and -1 ppm and applying off-resonance correction based on the frequency shift estimated during baseline off-resonance correction. The z-spectra were then converted to MTR_{sym} curves. The glucoseCEST enhancement (GCE) parameter was defined as the change in area under the MTR_{sym} curve following glucose injection, and was calculated on a pixel-by-pixel basis, using the average area under the MTR_{asym} curve during the first 10 minutes of the dynamic scan was used as the pre-injection intensity. GCE was converted to absolute glucose concentration using a linear calibration based on previously reported phantom measurements from glucose phantoms [3], assuming a tumor pH of 7.2.

Compartmental modelling: Glucose concentration (C(t)) data were fitted to the two-compartment model shown to the right, in which the blood plasma glucose concentration is modelled as a bi-exponential function of the form $C_p(t) = a_1\exp(-m_1t) + a_2\exp(-m_2t)$. The parameters a_1, m_1, a_2 and m_2 were derived from fits to measurements using a hand-held blood glucose monitor (Roche) from blood samples from the tail vein of six mice, at 30 second intervals prior to and following i.p. injection of glucose. Onset time t_0 was fixed at 10 minutes after contrast agent injection and K_{in} (the rate of extravasation of glucose from blood plasma to the interstitium) and V (the fraction of the voxel volume accessible to glucose) were estimated in each pixel and maps of each were produced. The area under the curve (AUC) was also measured for each pixel.

$$C(t) = K_{in}\sum_{i=0}^{1}\frac{a_i}{m_i-(K_{in}/V)}\left(e^{-m_i(t-t_0)}-e^{-K_{in}(t-t_0)/V}\right)$$

Results. Fits to blood plasma glucose samples gave parameter values of a_1 = -3.57 mM, m_1 = 0.15 /min, a_2 = 1.69 mM, and m_2 = -0.02, which were used as the AIF in all studies. Figure 1 shows example maps of K_{in}, V and AUC from an example SW1222 tumor xenograft model, which display a regionally heterogeneous uptake of glucose. Mean estimated K_{in} and V were 0.12 ± 0.08 /min and 0.68 ± 0.2, respectively. The former value agrees well with estimates of K^{trans} from similar measurements using gadolinium chelates [6]. Averaged curves with fits overlaid from three regions within the tumor are also shown. These data reveal transient variations in glucose uptake with a period of approximately 10 minutes that were also observed in tail vein sample curves. Oscillations in blood glucose concentration with comparable frequency in mice have been reported in the literature resulting from biphasic insulin secretion [7].

Discussion. This study provides a proof-of-principle that glucoseCEST can be used to estimate glucose pharmacokinetics, via two-compartment modelling. Parameter estimates from this technique was similar to those derived from similar studies with gadolinium chelates. The simple two-compartment model (representing blood plasma and extra-vascular space) used in this study could be advanced with the use of multiple compartment models to estimate cellular uptake and metabolism, although whether the technique offers sufficient sensitivity to support such analysis must be further investigated. Furthermore, oscillating features observed in glucose uptake curves, potentially consistent with a biphasic insulin response [7], may offer the potential for the evaluation of glucose tolerance.

Acknowledgements: King's College London and UCL Comprehensive Cancer Imaging Centre, CR-UK & EPSRC, in association with the MRC and DoH (England), British Heart Foundation. **References:** [1] Walker-Samuel *et al.*, Proc. ISMRM 2011, Montreal, #962, [2] Chan *et al.* Proc. ISMRM 2011, Montreal, #551, [3] Walker-Samuel *et al.* Proc. BCISMRM 2011, Manchester, [4] van Zijl et al., PNAS, 2006, 104(11), [6] Tofts *et al.*, J Magn Reson Imag 1999;10(3), [7] Nunemaker et al., Am J Physiol Endocrinol Metab, 2006;290.