Optimisation of the Bolus and Infusion Protocol for Equilibrium Magnetic Resonance Imaging

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Introduction

Changes in the fractional volume of the extravascular, extracellular space (V_{EES}) can be indicative of pathology, for example in oncology, V_{EES} has been shown to influence tumour aggressiveness and treatment response [1]. Equilibrium MRI (EQ-MRI) is a recently proposed technique to measure V_{EES} [2]. In EQ-MRI, a bolus of gadolinium based contrast agent (CA) is followed by a continuous infusion and after a period of time, a constant concentration of the CA is reached in the blood pool and tissue. The V_{EES} is then calculated: $V_{EES} = (1 - Hct)\frac{\Delta R_{1,tissue}}{\Delta R_{1,blood}}$ [2] (eqn. 1), where Hct is the haematocrit and ΔR_1 is the difference between the R_1 measured pre CA and R_1 at equilibrium, i.e. only two measurements of R_1 are required, given the equilibrium condition.

Aims

To 1) devise a pharmacokinetic model for EQ-MRI of the combined bolus and infusion (B/I) protocol in order to predict what infusion dose to use to achieve equilibrium as soon as possible, and 2) pilot the optimised protocol to measure V_{EES} in normal tissue to compare to reference values.

Methods

Pharmacokinetic model: A bi-exponential model was used for the plasma concentration of CA (C_p) after bolus injection [3][4]. An infusion was modelled by adding a constant dose to C_p, starting at t_{inf}, and re-evaluating the bi-exponential decay given the new value of C_p. The tissue concentration (C_t) was calculated as: $C_t(t) = C_p(t) \otimes K^{trans}e^{-kep\,t} + V_p C_p(t)$ [5] (eqn. 2) where K^{trans} is the rate constant of the CA into the tissue, $k^{ep} = K^{trans}/V_{EES}$ and V_p is the fractional plasma volume. A fixed bolus dose of 0.05mmol/kg was used and a maximum infusion dose of 0.05mmol/kg/hr to keep the total B/I dose within recommended limits (0.1mmol/kg). The infusion dose was varied iteratively between 0-0.05mmol/kg/hr in steps of 0.005mmol/kg/hr for a fixed K^{trans} of 0.5min^{-1}. The optimum protocol was chosen as one that achieved equilibrium in as shortest time as possible, and equilibrium defined as a variation in C_t of <0.01% between consecutive time points, for a period of 600s.

Experiments: 1) Data were collected in 3 controls with a bolus only to compare measured C_p with that predicted using the bi-exponential model. A baseline T1 measurement was followed by a bolus injection of Gd-DOTA (Dotarem,Guerbet) of 0.05mmol/kg at 3ml/s and rapid "dynamic" imaging (see below). Exp. 2) Data were collected in a single control subject using the optimised B/I protocol found via simulation, with a pre-bolus T1 measurement, a T1 measurement post infusion at the model predicted equilibrium time (t_{eq}), and a further two T1 measurements to asses if equilibrium had been reached. Imaging was performed at 1.5T (Avanto, Siemens Healthcare, Germany), using a VIBE sequence, TE/TR=0.8/2.6ms, voxel size=2x2x10mm, matrix size=144x192x40. All images were acquired during breath hold. For the dynamic imaging, repeated volumes were acquired with flip angle (FA)=15°, NSA=1. For T1 mapping, data were collected with 6 different FAs (5°,10°,15°, 20°, 25° and 30°), with NSA=5 at each FA. Processing: ROIs were drawn by a radiologist in the aorta, the liver and psoas muscle. The change in signal intensity in the aorta, ΔS, measured during the dynamic phase compared to baseline (S_0) was used to compute C_p: $C_p = \Delta SI/S_0\, T_{10}\, r\, (1 - Hct)$ (eqn. 3), where r is the relaxivity of the CA. The Ernest function was fitted to the multi-FA data using the Levenberg-Marquardt algorithm for T1 in each ROI [6], and V_{EES} was calculated with eqn. 1.

Results

For a bolus only, with a dose of 0.05mmol/kg, the simple bi-exponential model predicts plasma concentrations well for t>300s, but as expected, does not account for the earlier AIF (fig. 1). With this bolus only model, a reduction in plasma concentration of 23% is predicted between 600-1200s. Simulations show that an infusion dose of 0.025mmol/kg, started at t_{inf}=300s, achieves equilibrium at 614s in a tissue with K^{trans} of 0.5min^{-1} (fig. 2). For this infusion dose, t_{eq} is between 597-674 for a range of K^{trans} values from 0.1-2.0 min^{-1}, as expected in normal muscle and liver [7][8] (K^{trans} values of 0.1-1.0 min^{-1} are shown in fig 3). Measured T1 values at 600, 900 and 1200s are plotted in fig. 4 and the coefficient of variation (CoV) over the 3 time points, for the two tissues studied are given in table 1.

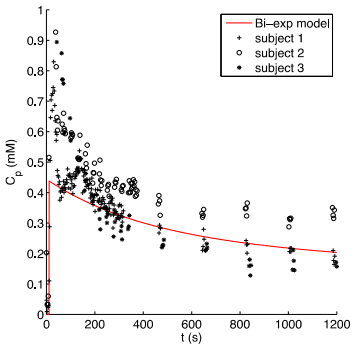

Figure 1. Simulated and measured plasma concentrations for bolus only

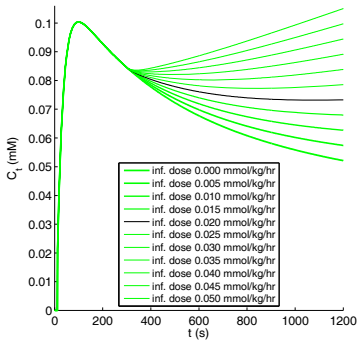

Figure 2. Simulated tissue concentrations for range of infusion doses (fixed K^{trans})

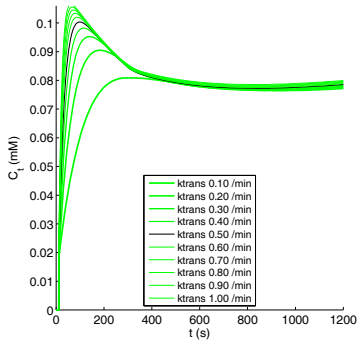

Figure 3. Simulated tissue concentrations for range of K^{trans} (fixed infusion dose)

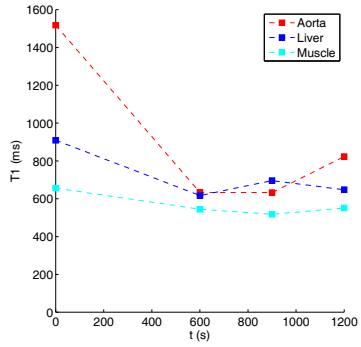

Figure 4. Measured T1 for bolus and infusion protocol

	T_1 CoV (%)	V_{EES} EQ-MRI	V_{EES} DCE
Liver	3	0.33	0.2-0.4 * [7]
Muscle	6	0.20	0.24±0.10 [8]

*Table 1. CoV of T1 values measured at 600, 900 and 1200s. V_{EES} EQ-MRI is calculated from T1 measured at 600s. *values estimated from graphical data*

Discussion and Conclusion

Dynamic Contrast Enhanced (DCE) MRI is an alternative MRI method to estimate V_{EES}. However DCE requires knowledge of the arterial input function, which can be difficult to measure or model, and therefore lead to imprecision of the V_{EES} estimate. In summary, model simulations of the B/I protocol predicted that with a bolus of 0.05mmol/kg and infusion of 0.025mmol/kg/hr, starting at 5 minutes, an equilibrium could be achieved for a range of K^{trans} values within approximately 10 minutes. The measured T1 values post 10 minutes are within a 6% CoV, in liver and muscle in our test subject, suggesting a steady state equilibrium is reached as predicted by the model.

References

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