Is it possible to measure water exchange using conventional DCE-MRI?

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Introduction. In recent years, there has been interest in how water exchange might affect tracer kinetics experiments performed using dynamic contrast-enhanced (DCE) MRI [1,2]. Most evidence to date suggests that vascular-interstitial water exchange is relatively slow (less than 7 s^{-1} [1]). There is no consensus on the rate of cellular-interstitial (also known as transcytolemmal) water exchange. Landis et al. [2] have suggested that this exchange may significantly influence the assessment of contrast agent concentration ([Gd]) in DCE-MRI experiments. Contrast agent enters the interstitium from the plasma and increases the relaxation rate of interstitial water while the T_1 of water in the cell remains the same; this may lead to significant transient sorties away from the pre-contrast water exchange state. Such an effect can result in underestimates in [Gd] and subsequent inaccuracies in estimates of tracer kinetics parameters [2]. Whether these effects are significant in a typical DCE-MRI experiment is the subject of debate.

MR signals obtained from muscle are potentially sensitive to cellular-interstitial water exchange and the small vascular volume of muscle minimizes the confounding effects of vascular-interstitial water exchange. Following the lead of Landis et al [2], we undertook a study of human muscle to address two principal aims. Firstly, we assessed the maximum possible effects of cellular-interstitial water exchange on measurements of tracer kinetics parameters obtained using a clinically-relevant DCE-MRI protocol by analyzing our data using fast exchange limit (FXL) and slow exchange limit (SXL) models. Secondly, we used the shutter-speed (SS) approach [2] (also called BOLERO [3]) to estimate the rate of cellular-interstitial water exchange in muscle.

Methods. Six patients (aged 60-77 years, mean 68 years) undergoing MRI for the assessment of benign prostatic hyperplasia were examined [4]. The study was performed at 1.5 T (Philips Intera) using a cardiac phased-array coil for signal detection. A volume including the prostate and internal obturator muscles was selected for quantitative imaging. The T_1 of tissues in this volume was measured using a multi-shot 3D IR-TFE sequence. Subsequently, a 3D FLASH sequence with a 30° flip angle and 3.4 ms TR was used to acquire volumes every 1.5 s for 7.5 minutes following injection of 0.1 mmol/kg Gd-DTPA-BMA. This was injected at 3 ml/s and after the dynamic run a further 10 volumes were acquired at 50°, 5° and 30°.

An arterial input function (AIF) was obtained from the external iliac arteries assuming a baseline blood T_1 of 1400 ms and a volume of muscle tissue was selected for further analysis. Model fitting was performed using a sequential quadratic programming algorithm (MATLAB). FXL, SXL and SS models in combination with a standard single-compartment tracer kinetics model [5] were each fitted to the raw 30° dynamic signal-time curves only using the measured AIFs and baseline T_1 estimates. This produced 3 estimates of K^{trans}: K^{trans}(FXL), K^{trans}(SXL) and K^{trans}(SS); 3 estimates of v_e: v_e(FXL), v_e(SXL) and v_e(SS) and 1 estimate of the intracellular residence time of water, t_i: t_i(SS). Precision of these estimates was assessed using a bootstrap technique [6]. To address concerns raised following the above comparisons a full 2-pool (cell & interstitium) exchange model was fitted simultaneously to all the post-contrast data (30° dynamic and 50°, 5° and 30° data) to provide estimates of K^{trans}(full), v_e(full) and t_i(full).

Results. Baseline T_1 of muscle was estimated to be 1060 ± 30 ms. Both the FXL and SXL models produced acceptable fits to the data, mean estimates of K^{trans}(SXL) were 7% higher than K^{trans}(FXL) and mean estimates of v_e(SXL) were 9% higher than v_e(FXL). Fits obtained using the SS model resulted in slightly decreased χ^2 compared to the FXL and SXL model fits in 3 of 6 cases but these were not statistically significant. Fits to the 2-pool model compared well with those obtained using the SS model but the estimates of K^{trans}(full) and v_e(full) were closer to those obtained using the FXL and SXL models than those obtained using the SS model (Table 1). Estimates of t_i(full) ranged from 0.5 to 4.2 s, were generally imprecise, and differed from t_i(SS) estimates (that ranged from 0 to 1.6 s).

Table 1. Mean (± SD) of parameter estimates obtained in 6 subjects using 4 different exchange models.

	K^{trans} ($\times 10^{-3}$ min^{-1})	v_e (no units)	t_i (s)
FXL	45 ± 25	0.13 ± 0.04	-
SXL	49 ± 27	0.14 ± 0.04	-
SS	67 ± 48	0.23 ± 0.14	0.69 ± 0.61
2-pool	47 ± 26	0.14 ± 0.04	2.6 ± 1.3

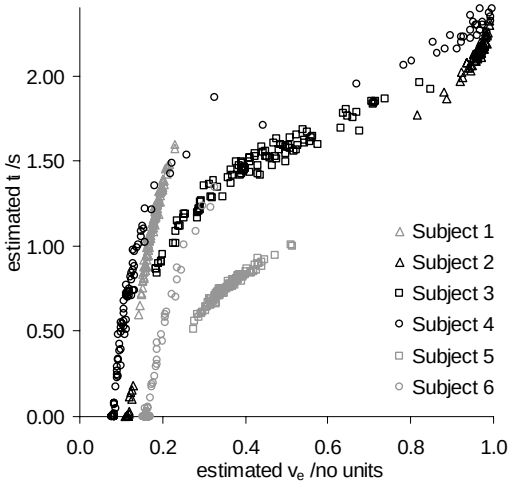

Fig. 1. Distribution of bootstrap estimates of v_e(SS) and t_i(SS). Note the poor precision in t_i(SS) for all subjects and poor precision in v_e(SS) for 3 (black symbols).

Discussion. The influence of cellular-interstitial water exchange on the measurement of [Gd] in muscle in our study was small. Despite the fact that FXL/SXL analyses represent the min./max. possible effects of cellular-interstitial water exchange and that estimates of K^{trans}(FXL) & K^{trans}(SXL) and v_e(FXL) & v_e(SXL) were precise, the error bars on these pairs of measurements typically overlapped. The SS model produced contradictory results. Estimates of both K^{trans}(SS) and v_e(SS) lay above the upper limit determined by the SXL results in half the cases. Furthermore, the error bars on the estimates of v_e(SS) and, in particular, t_i(SS) were often excessively large. Examination of the bootstrap fits revealed strong correlations between estimates of v_e(SS) and t_i(SS) in half the cases (Fig. 1) and between v_e(SS) and K^{trans}(SS) in 2 others. The t_i(SS) estimate obtained in the remaining case was 0 s; in this limit SS ≡ FXL. These results raise questions about the validity of the SS approach when applied to clinical DCE-MRI data; FXL and SXL models may be better choices for an assessment of tracer kinetics parameters. The full 2-pool model was able to estimate t_i(full) while maintaining estimates of K^{trans}(full) and v_e(full) within the bounds of the FXL and SXL models. However, the estimates of t_i(full) were imprecise and had a high inter-subject variability. Future studies will require more exchange sensitive data.

Using a conventional DCE-MRI acquisition, data were obtained from the internal obturator muscle in an exchange minimized manner. Analysis of such data using a SS approach should be approached with caution as estimates of K^{trans} and v_e may be biased, estimates of t_i may be inaccurate and many parameter estimates are likely to be imprecise. Though it was possible to estimate t_i using data with a range of flip angles and a 2-pool model, these estimates were very imprecise and suggest that DCE-MRI data of this type - used in isolation - are unsuitable for the assessment of water exchange.

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