Pseudo Extravasation Rate Constant of Dynamic Susceptibility Enhanced Magnetic Resonance Imaging Determined From Pharmacokinetic First Principles

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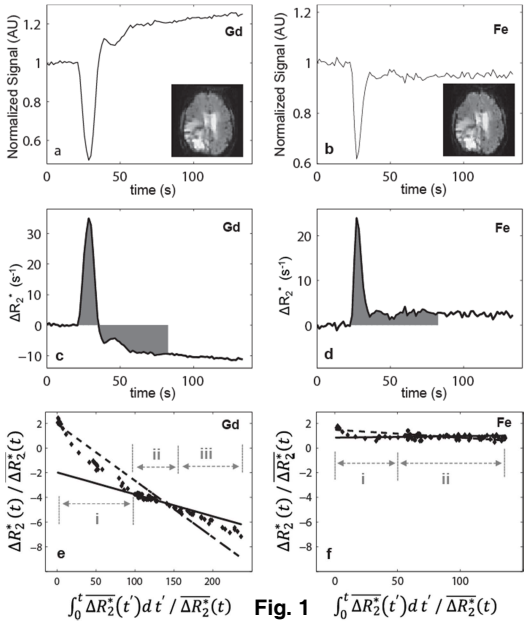
Purpose: Though widely adopted for brain perfusion measurement, Dynamic Susceptibility Contrast (DSC) Magnetic Resonance Imaging (MRI) with low molecular weight Gadolinium (Gd; ~600 Da) contrast reagent (CR) is often confounded by CR leakage into intersitium space. Based on pharmacokinetic first principles, we demonstrate a fast leakage correction method similar to Gjedde-Patlak plot (1,2) linearization that uniquely identifies the leakage rate and significantly simplifies relative cerebral blood volume (rCBV) quantification.

Methods: Seventeen subjects with GBM were prospectively studied on institutional review board approved protocols. Subjects underwent two consecutive days of MRI scans on a Siemens TIM Trio scanner. On the first day, DSC-MRI were acquired using gadoteridol (ProHance, Bracco Diagnostic Inc.). On the following day, the same MRI sequences were acquired using the high-molecular weight (750 kDa) iron-based CR, ferumoxytol (provided by AMAG Pharmaceuticals, Inc.). The DSC employed a gradient-echo echo-planar imaging pulse sequence (TR/TE/FA: 1500 ms/20 ms/45°, field of view 192 x 192 mm^2, matrix 64 x 64, and 27 interleaved slices). The contrast reagent was administered intravenously after the 7th image frame using a power injector (Spectris Solaris - MEDRAD Inc., PA) followed immediately by 20 mL of saline flush.

Based on the simple assumption that the extravasating and intravascular Gd introduced R_2* change can be linearly combined (3,4), the pixel ΔR_2* time-course accounting for an intravascular contribution and an extravasating component can be simplified to Eq. (1),

$$\Delta R_2^*(t) \approx K_1 \overline{\Delta R_2^*}(t) - K_2 \int_0^t \overline{\Delta R_2^*}(t')\,dt' \qquad (1)$$

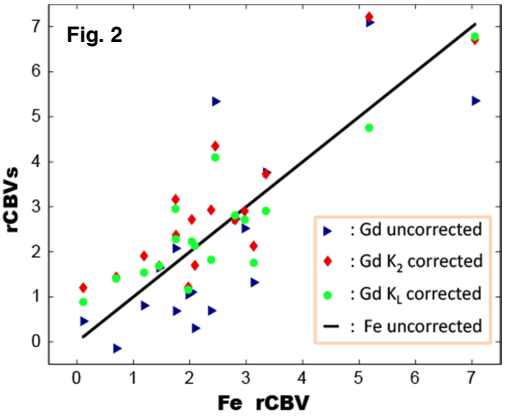
ΔR_2* represents the pixel time-course for R_2* change, K_1 and K_2 are proportional constants for intravascular and extravasating contributions to ΔR_2*, respectively. $\overline{\Delta R_2^*}(t)$ is the time-course of blood R_2* change, approximated by combining signal changes from all non-leaking pixels (4) available within the imaging slice or volume.



$\int_0^t \overline{\Delta R_2^*}(t')dt' / \overline{\Delta R_2^*}(t)$ **Fig. 1** $\int_0^t \overline{\Delta R_2^*}(t')dt' / \overline{\Delta R_2^*}(t)$

Fundamental pharmacokinetic theorem predicts if K_2 is a pseudo-first order rate constant reflecting CR extravasation, its value and pharmacokinetic meaning can still be well identified through pharmacokinetic first principles. With a linear transform (1,2) of equation (1) similar to Patlak plot, we can identify a leakage constant, K_L, uniquely. Here K_L differs from K_2 in that K_L is only calculated from the linear portion after the transformation.

Results: **Fig. 1**. 1a and 1b show same subject co-registered pixel intensity time-courses from enhancing lesion area for Gd and Fe CRs, respectively. Insets in 1a and 1b display corresponding same frame co-registered post-injection dynamic images. The signature "leakage effect" of post-CR signal increase to above baseline due to T_1 shortening is evident in 1a Gd time-course, but not in intravascular Fe (1b). Calculated ΔR_2* from 1a time-course resulting in an artificial dipping of ΔR_2* below zero (1c). Shaded area illustrates numerical integration of ΔR_2* underestimates rCBV value. This is not seen with nano-sized intravascular Fe CR in 1d. Figure 1e symbols show the same pixel data from 1a underwent Patlak style linear transform and plotted with respective coordinates as labeled. The solid line is from a linear regression of the transformed data points from 100 to 140 on Fig. 1e abscissa scale, reflecting a range of 40s -70s post-CR on the DSC time-course. The dashed line is with the slope equals to K_2 determined from fitting Eq. (1) with all data points up to 70 s post CR injection. The plot can be roughly divided into three regions: i, transient period of CR first pass; ii, pseudo equilibrium period where linearity obtains; iii, intravasation/linearity deviation period, where graphed data points clearly deviate from linear trend, most likely due to Gd CR intravasation. With no CR extravasation, linear transformed plot of the intravascular Fe data in 1f shows no departure from the linear trend after its establishment even towards the end of the DSC time-course. Here, there is no visible period iii for intravasation. Lesion region-of-interest (ROI) data are summarized in **Fig.2**. It plots the three Gd rCBVs vs. Fe rCBVs (solid line, unit slope) for all 17 subjects included in the study: rCBVs from Gd without leakage correction (▶); leakage corrected rCBVs using Eq (1) fitted K_2 leakage rate constant (◆); and leakage corrected rCBVs using the K_L leakage rate constant derived from the linear portion of the "Patlak" transformed data(●). While the uncorrected Gd rCBVs under-estimate, the Eq. (1) fitted K_2 often overestimate. The relatively more evenly distributed rCBVs with K_L leakage correction around the solid line empirically demonstrate its better performance.



Discussion: Though Eq. (1) is not a pharmacokinetic equation, we demonstrated that a linear transform similar to Patlak plot can be used to better define Gd CR leakage rate in DSC MRI. It simplifies DSC rCBV quantification and provides pharmacokinetic insights of K_L, which differs from K_2 leakage constant in literature (4) and FDA 510K cleared package (5) available for DSC quantification.

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