Leakage and Water Exchange Characterization of Gadofosveset in the Myocardium

Octavia Bane[1,2], Daniel C Lee[3], Brandon C Benefield[3], Kathleen R Harris[1], Neil R Chatterjee[2,3], James C Carr[1], and Timothy J Carroll[1,2]

[1]*Radiology, Northwestern University, Chicago, IL, United States,* [2]*Biomedical Engineering, Northwestern University, Evanston, IL, United States,* [3]*Medicine, Northwestern University, Chicago, IL, United States*

Purpose

Quantification of myocardial blood volume (MBV) can potentially characterize compensatory dilation of microvessels that occurs distal to a coronary stenosis ***at rest***, raising the possibility of coronary artery disease detection without the need of a provocative stressor (1). In order to accurately quantify fractional myocardial blood volume (fMBV), a parameter that has been used to calibrate first-pass blood volume measurements (2), we compared the compartmentalization of two blood pool agents and validated our results in simulation, animal and human studies.

Methods

Volunteer study: Five healthy volunteers (4 males, average age 33) underwent T_1 on a 1.5T Espree scanner (Siemens) measurement pre and 2 minutes post administration of five injections of 0.006 mmol/kg (a fifth of a single dose) of gadofosveset (Ablavar, Lantheus Medical Imaging). Steady-state T_1 was mapped using a cardiac gated Modified Look Locker Inversion Recovery (MOLLI)(3) pulse sequence (slice thickness 8 mm, FOV 300 x 400 mm^2, matrix 256x172, TE 1.14 ms, TR 2.25 ms,effective TI 100 ms). Maps of fractional blood volume (fv, %) were calculated from signal difference maps, according to a slow water exchange model(4). Fv was measured in the myocardium, dome of the liver, and skeletal muscle visible on the short axis MOLLI images, and was corrected for Ablavar extravasation based on the simulation study of partial binding. The true fv and exchange rate of water protons was determined by Chi Square minimization between data and simulations of the effect of water exchange on fv according to the two compartment water exchange model presented by Donahue et al.(4).

Simulation Study**:** In vitro studies have shown Ablavar to be 80-90% bound to albumin, with up to 5 fold relaxivity difference between bound and free fractions. We performed simulations to assess the effect of extravasation of the free fraction on signal. Vascular fraction measurements were simulated assuming slow (fv= ΔS myocardium/ΔS blood) and fast (fv= ΔR_1myocardium/ΔR_1 blood) two-compartment exchange for different contrast agent injection concentrations, binding fractions, bound and free relaxivity, and true vascular fractions.

Comparison with USPIO**:** A 16 kg instrumented dog was imaged using the USPIO contrast agent ferumoxytol (Feraheme, AMAG Pharmaceuticals) diluted from 30 mg elemental iron (Fe)/ml solution to 5.3 mg Fe/ml. One injection bolus of 6 ml (2 mg/kg), followed 13 minutes later by two 3 ml injections (1 mg/kg) 4 minutes apart, were administered via power injector at the rate of 4 ml/sec. MOLLI images in the short-axis view (slice thickness 8 mm, FOV x mm^2, matrix 256x108, TE 1.19, TR 2.75, effective TI 100 ms, TI increment 80 ms, 11 acquisitions) were acquired every minute for 13 minutes after the first injection, and 3 minutes after the last two injections . T_1 was measured off T_1 maps, generated in MATLAB by a three-variable fit (Figure 1). In a retrospective study, fMBV slow exchange was mapped by the same procedure as used in the human volunteers. fMBV fast exchange was calculated from T_1 values.

Results

We found that the effect of partial binding of Ablavar on the measurement of vascular fraction is less that 20%. The true vascular fractions and compartment residence times, are summarized in Table 1. A comparison of the myocardium relaxation rate induced by administration of Ablavar in healthy volunteers imaged at 1.5 T, with other extracellular and intravascular contrast agents (5,6) shows that Ablavar behaves like an extracellular contrast agent (Figure 2).

fMBV measured in the canine subject in the slow and fast exchange limits

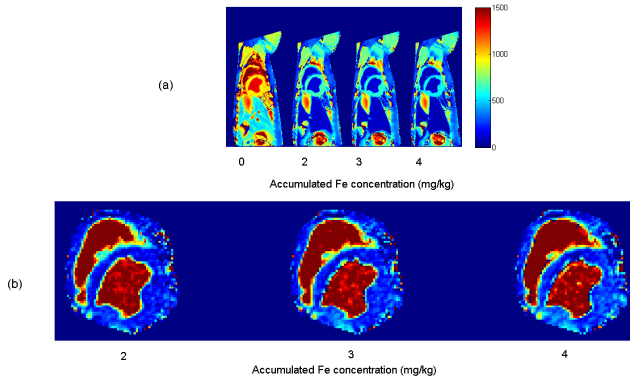

Figure 1. a) T_1 (ms) and b) fMBV slow exchange maps, before and 3 minutes after repeated injections of ferumoxytol in a canine subject.

Discussion and Conclusions

The measured values in volunteers of fv in liver and muscle agree with the Donahue model. Measured myocardial fv values over-estimate published values (9-12%), and approach those of extracellular volume (22-25%), which suggests the intravascular assumption may not be appropriate for Ablavar. The distribution of the volunteer data in Figure 2 indicates that a three-compartment model, with slow exchange of Ablavar and water protons between the vascular and interstitial compartments, and fast water exchange between the interstitium and the cells (5) is appropriate.

The true fMBV values measured in the animal with ferumoxytol of 5%, true τ= 22 msec in the slow exchange limit, and 7% with τ= 877 msec for the fast exchange limit, agree with published values (7). Ferumoxytol data is also within the bounds predicted by the slow and fast exchange limits of the two compartment model. This points to ferumoxytol as a truly intravascular agent in the myocardium, suitable for MBV quantification.

Table 1

	Measured fv (%)	Measured exchange rate (Hz)	Fv slow exchange (%)	Fv fast exchange (%)
Myocardium	22	1000	-	-
Liver	45	3.7	41± 6	26±7
Muscle	16	1	8±3	15±1

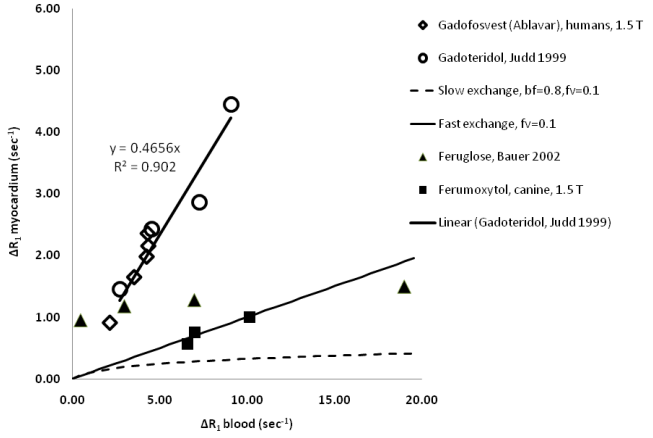

Figure 2. Comparison of Ablavar with other contrast agents. Ablavar aligns with the model developed by Judd et al. (1999) for an extracellular agent undergoing limited contrast agent and water exchange between the intravascular and interstitial space, and fast interstitial-intracellular water exchange.

References

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