Measurement of quantitative myocardial blood volume and water exchange using ferumoxytol

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Purpose: Accurate, quantitative measurements of myocardial blood volume (MBV) could potentially serve as a novel biomarker for cardiovascular disease. However, quantitative measurement of MBV is confounded by exchange between the intravascular and extravascular compartments. With typical gadolinium based contrast agents, the contrast agent itself leaks out of the vasculature and into the extracellular space. Even with completely intravascular agents, water exchange between the intravascular and extravascular compartments has been shown to introduce error into blood volume measurements [1]. The Hazlewood two compartment model [2] has been used to describe water exchange in MR relaxation, and Donahue et al [1] adapted this model to quantify the error that water exchange introduces into blood volume measurements. Here we ferumoxytol, a wholly intravascular contrast agent, and the Hazlewood two compartment model to characterize water exchange and quantify MBV in a group of healthy volunteers

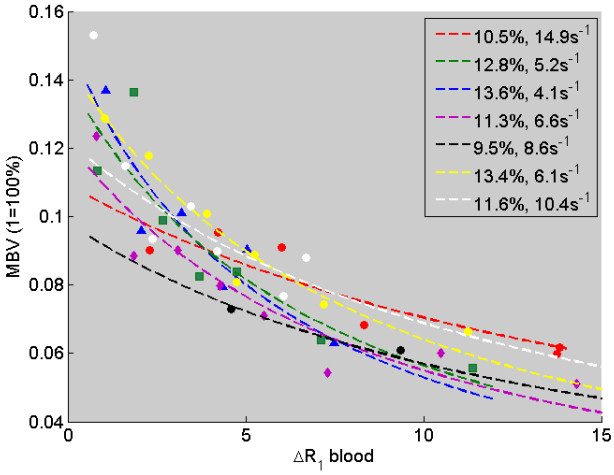

Figure 1: Blood pool relaxivity vs apparent MBV in a cohort of healthy volunteers. Points are experimentally measured data, and dashed lines are best fit simulations from the Hazlewood two-compartment model. The true MBV and exchange frequencies from the best fit simulations are show in the legend.

Methods: 7 healthy volunteers were recruited for this study. Each volunteer received multiple small boluses of ferumoxytol (Feraheme). Prior to and after each bolus, modified Look Locker (MOLLI) images were acquired in a single mid-cavity short axis slice (flip angle 35, TE 1.12, 212x256 matrix, 1.4x1.4 pixel size, 8mm slice thickness). All scanning was done on a 1.5T scanner (MAGNETOM Aera, Siemens AG, Erlangen, Germany). T1 images were constructed online by the MOLLI sequence. Mean T1 values were then extracted from blood pool and septal regions of interest for each image. These T1 values were then used to calculate apparent MBV (ΔR1 myocardium / ΔR1 blood) for each image.

The Hazlewood two compartment model was then simulated in MATLAB. The Hazlewood model simulation calculates apparent MBV (ΔR1 myocardium / ΔR1 blood) as a function of ΔR1 blood, the true MBV (the actual MBV independent of exchange effects), and water exchange frequency. The true MBV and exchange frequency for each subject was then calculated by fitting the experimentally measured apparent MBV vs ΔR1 blood data to the simulated apparent MBV vs ΔR1 blood curves generated by the Hazlewood model. The fitting was done using a least squares minimization algorithm.

Results: Experimental data and best fit exchange curves are shown in Figure 1. True MBV was 11.8 $\pm$ 1.5% and water exchange frequency was 8.0 $\pm$ 3.7 s^{-1}.

Discussion: We were successfully able to measure MBV and water exchange in they myocardium of healthy volunteers. Our average MBV of 11.8% and average exchange frequency of 8.0 s^{-1} are in good accordance with values of 6-12% and 5-9s^{-1} seen in the literature for animal studies[1,3-5]. From Figure 1, it is clear that as blood pool relaxivity increases there is considerable error in the uncorrected MBV measurement, with apparent MBV frequently half the true MBV. Without correction for water exchange, these errors would manifest as scan-scan variability and systematic underestimation of MBV.

The mean MBV and exchange rates calculated here are in contrast to similar work done previously using gadofosveset (Ablavar)[6]. In those experiments, the measured "MBV" and exchange rates were much higher, and these values were theorized to actually represent extracellular volume and intracellular-extracellular water exchange. That we were able to achieve different results here with similar methods but using a different contrast agent supports the theory that gadofosveset in those experiments did not behave as an intravascular agent during first pass.

Conclusions: Water exchange introduces significant errors in MBV measurements, but by using serial injections of an intravascular agent, this error can be simulated and the true MBV quantified. More work is needed to investigate the relationship between quantitative MBV and cardiovascular disease.

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