Quantitative MRI of the Myocardial Microcirculation in Mice using FAIR Look-Locker Arterial Spin Labeling and a Gamma-variate Model of Blood Transit Time Distribution

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Introduction: Experimental therapies for ischemic heart disease (IHD), such as stem cells, injectable biomaterials, and gene transfer, are widely investigated in mouse and rat models. For these investigations, a multi-parametric assessment of the microcirculation would be highly valuable. Arterial spin labeling (ASL) has previously been used to quantify myocardial blood flow (MBF) in small animals. This technique typically uses a flow-sensitive alternating inversion recovery (FAIR) preparation followed by an ECG-gated Look-Locker acquisition to measure longitudinal relaxation at a sequence of times after slice-selective (SS) and non-selective (NS) inversions (e.g.(1)). While data analysis for ASL of the rodent heart has previously computed MBF by calculating a shift in T_1 between SS and NS curves (1,2), these images could be more comprehensively analyzed using a kinetic model (3,4). In the present study, we developed a kinetic analysis for ASL based on a gamma-variate blood transit model, and performed an initial evaluation of this method for Look-Locker ASL of mice, quantifying MBF, myocardial blood volume (MBV), and mean transit time (MTT) in normal and vasodilated animals.

Methods: Seven mice (3 at rest and 4 with the vasodilator ATL313, 18.75μg/kg) underwent cardio-respiratory gated (CRG) FAIR Look-Locker ASL of the heart using a 7T small-bore scanner (Clinscan, Bruker, Germany), as recently described (1). For FAIR Look-Locker ASL, upon detection of a CRG trigger either a SS or NS inversion was performed. For 50-60 triggers after the inversion, an RF pulse was applied and a corresponding gradient-echo was acquired. A delay of 6-8 seconds elapsed between inversions, and the pulse sequence was repeated until all raw data were acquired. Other parameters included flip angle = 3°, slice thickness=1mm, averages=3, and pixel size = 240x240 μm^2. Using this sequence, the SS and NS longitudinal relaxation curves of the myocardium, $M_{SS}(t)$ and $M_{NS}(t)$, were measured. One short-axis plane was scanned, with an acquisition time of 1 hour.

For image analysis, a solution to the fundamental ASL differential equation (5) was developed that uses a gamma-variate function to model the distribution of blood transit times through the myocardium and to generate the arterial blood magnetization function, $M^A_{SS}(t)$. A gamma-variate distribution has long been used to accurately represent the blood transit time spectrum of a vascular bed (6), but has not previously been used to analyze kinetic ASL data. If we define the difference function $D(t) = M_{SS}(t) - M_{NS}(t)$, and we let $1/T_1' = (1/T_1) + f/\lambda$, where f is MBF, T_1 is the relaxation time of myocardium, and λ = 0.95 is the blood/tissue partition coefficient, then the gamma-variate-based solution to the ASL equation can be shown to be:

$$D(t) = 2 \cdot f \cdot M^0_B \cdot M^A_{SS}(t) \cdot e^{-t/T_{1b}} * e^{-t/T_1'} \quad \text{where} \quad M^A_{SS}(t) = \int_{\tau=0}^{t} h(\tau) \cdot d\tau \quad \text{and} \quad h(t) = \left(t - t_{delay}\right)^{\alpha} e^{-(t-t_{delay})/\beta}$$

For these equations, M^0_B is the proton density of blood, $M^A_{SS}(t)$ is the arterial blood magnetization after a SS inversion, T_{1b} is the T_1 of blood, $h(t)$ is the blood transit time distribution (impulse response) with the form of a gamma-variate, α determines the upslope of $h(t)$, β determines the decay of $h(t)$, and t_{delay} determines the transit delay of $h(t)$. By measuring $D(t) = M_{SS}(t) - M_{NS}(t)$ using Look-Locker or multi-TI ASL and performing an optimal 4-parameter fit of $D(t)$, MBF and $h(t)$ are determined. From the moments of $h(t)$, the MTT is computed. Using the central volume principle, MBV = MBF x MTT.

Results: Example frames from a SS Look-Locker image series of the mouse heart are shown in Fig. 1, and demonstrate typical image quality. Fig. 2A shows example $M_{SS}(t)$ and $M_{NS}(t)$ curves from the myocardium normalized to M^0_B, where the affect of inflowing arterial water causes an observable change in the $M_{SS}(t)$ curve compared to the $M_{NS}(t)$ curve. The difference data, $D(t)$, for this example are plotted in Fig. 2B along with the optimal gamma-variate-based model solution. For this example of a vasodilated mouse, we found MBF = 11.4 ml/min/g, MBV = 7.3 ml/g, and MTT = 380 ms. Mean results for all mice (Table 1) show a significant increase in MBF with vasodilation and a trend toward increased MBV under this condition.

Conclusions: A novel solution was developed for kinetic ASL that uses a gamma-variate distribution as the underlying model of blood transit through the vascular bed of the heart. This model is consistent with prior cardiovascular literature from other modalities (6-8), and theoretically reflects vascular physiology better than other models such as Gaussian or plug flow (7,8). The application of this solution to Look-Locker ASL of the mouse heart quantified resting values of MBF, MBV, and MTT, and demonstrated an increase in MBF and a trend toward an increase in MBV during vasodilation. Kinetic ASL with a gamma-variate-based model of the blood transit time distribution shows promise for quantifying multiple parameters of the microcirculation in the mouse heart. The use of compressed sensing is being explored to reduce data acquisition times in the future.

References: [1] Vandsburger et al. MRM 2010 Mar;63(3):648-57. [2] Belle et al. JMRI 1998;8:1240–1245. [3] Buxton et al. MRM 1998 Sep;40(3):383-96. [4] Hrabe et al. JMR 2004 Mar;167(1):49-55. [5] Detre et al. MRM 1992 Jan;23(1):37-45. [6] Thompson et al. Circulation Research 1964 Jun;14:502-15. [7] Davenport et al. Journal of Nuclear Medicine 1983 Oct;24(10):945-8. [8] Harpen et al. Medical Physics 1984 Sep;11(5):690-2.

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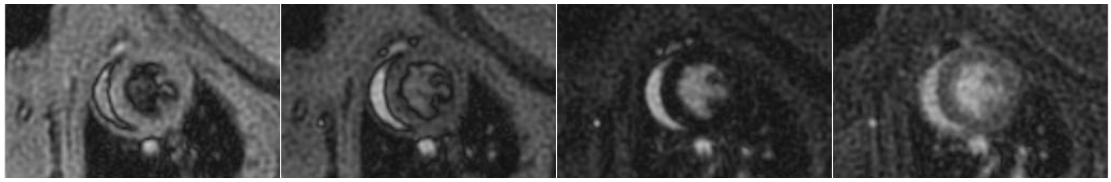

Fig. 1. Example Look-Locker images of the mouse heart at sequential times after slice-selective inversion.

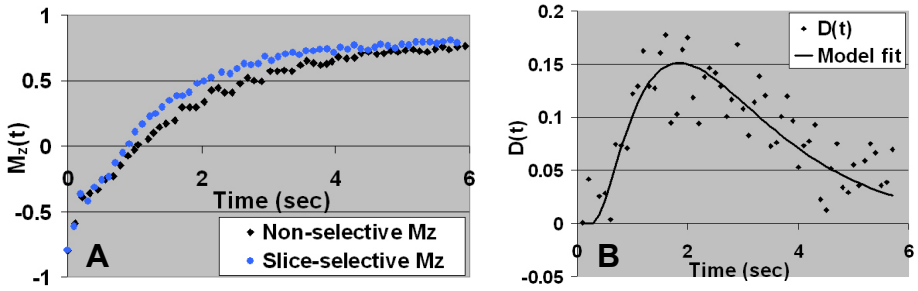

Fig. 2. (A) Myocardial $M_z(t)$ measured by Look-Locker ASL after NS and SS inversions. (B) $D(t)$ and the optimal gamma-variate-based model fit to $D(t)$.

Parameter	Rest	ATL313
MBF (ml/g/min)	5.4±2.0	11.2±3.1*
MTT (ms)	445±151	442±260
MBV (ml/g)	4.3±2.4	7.9±5.2

Table 1. Microcirculation parameters at rest and at vasodilation. (* p<0.05)