In Vivo Measurement of Blood Transit Time in Rat Brain using the Saturation Recovery-T1app Imaging Method

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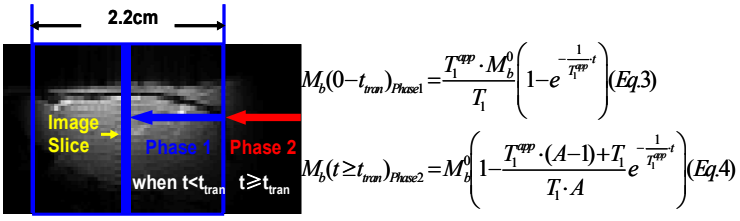
Introduction: The blood transit time (t_{tran}) in the brain is a very important physiology-related parameter, which may potentially reflect the status of hemodynamic impairment in cerebrovascular disease like ischemia and stroke. In the present study, we aim to determine the transit time in the rat cortex using the Saturation Recovery T_1^{app} (SR-T_1^{app}) measurement and two-phase spin model.

Theory: The modified Bloch equation linking the brain water magnetization and flow effects can be described as: $dM_b/dt = (M_b^0 - M_b)/T_1 + f \cdot M_a - f \cdot M_b/\lambda$ (Eq.1)[1], where M_b is the longitudinal magnetization of brain tissue and it becomes M_b^0 at fully relaxed condition; T_1 is the brain tissue longitudinal relaxation time in the absence of blood flow; f refers to the cerebral blood flow (CBF); λ (=0.9ml/g) is the blood-tissue water partition coefficient. The apparent longitudinal relaxation rate R_1^{app} ($1/T_1^{app}$) of brain tissue and CBF have a relation according to $R_1^{app} = R_1^{int} + f/\lambda$ (Eq.2), where R_1^{int} stands for intrinsic R_1 which is insensitive to physiology change therefore can be treated as a constant. The diagonally hashed region within the blue box in Fig. 1 depicts the saturated region in the rat brain. The right side of the figure is proximal to the heart. Assuming the arterial blood spins travel as bulk flow at a constant speed without turbulence, within the time period of 0-t_{tran} (defined as Phase 1), the flowing spins within the saturated region will reach the image slice. In contrast, the arterial spins outside of the saturated region will take a longer time of $\geq t_{tran}$ (Phase 2) to arrive at the image slice of interest. Since transit time in a normal rat brain is within a range of 100 to 400 ms[1-5], which is much short compared with the blood T_1 value (about 2.38 sec at 9.4T)[6], the recovered M_a is negligible (i.e., $M_a \approx 0$) when $t < t_{tran}$ and $M_b(0)=0$. These preconditions were used to solve Eq. 1, resulting in Eq. 3 for Phase 1. Eq. 4 is the solution of Eq. 1 for Phase 2 using $M_a = M_b^0/\lambda$ (consider water as a freely diffusible tracer) and the boundary magnetization of $M_b = M_b(t_{tran})$, where $A = \exp(-R_1^{app} \cdot t_{tran})$. It is important to note that although the modulus in Eqs. 3 and 4 are slightly different, the magnetization generally decays with the same rate of R_1^{app} during Phase 1 and Phase 2



$$M_b(0-t_{tran})_{Phase1} = \frac{T_1^{app} \cdot M_b^0}{T_1}\left(1 - e^{-\frac{1}{T_1^{app}} \cdot t}\right) \quad (Eq.3)$$

$$M_b(t \geq t_{tran})_{Phase2} = M_b^0\left(1 - \frac{T_1^{app} \cdot (A-1) + T_1}{T_1 \cdot A} e^{-\frac{1}{T_1^{app}} \cdot t}\right) \quad (Eq.4)$$

Figure 1 Schematic diagram of the two-phase spins model for global SR-T_1^{app} measurement overlaid on a sagital anatomic rat brain image. Eq.3 (phase1) and Eq.4 (Phase 2) are solutions for modified Bloch equation (Eq.1).

Material and MRI method: MRI experiments were carried out in a horizontal 9.4T animal magnet. An 8-shape surface coil (2.8cm×2cm) was used to acquire rat brain images. Animal anesthesia was maintained at 2% isoflurane. Hypercapnia was induced by switching to an inhalation bag with mixed gases (6% or 3% CO_2, 34% O_2, 58% N_2O and 2% isoflurane). All the R_1^{app} images were acquired before (i.e., normocapnia or control) and during stable hypercapnia condition when the animal physiology was within a normal range. Gradient echo EPI (TE=21ms; FOV=3×3cm; image matrix=64×64; 2 mm thickness) combined with the global saturation recovery or slab saturation preparation was used for imaging T_1^{app} with nine varied saturation recovery times (T_{SR}) of 0.008, 0.1, 0.2, 0.3, 0.4, 0.5, 1.4, 3 and 10 s. ROI data taken from the rat somatosensory cortex were used to perform the R_1^{app} regression analysis. MRI data analysis was performed using the Matlab software package. Based on Eqs. 3-4, a series of simulated signal intensity time courses with varied transit times (in 10-ms steps) were generated using the R_1^{app} and R_1^{int}values measured in this study and then compared them to the experiment signal time courses as a function of T_{SR}. The transit time was determined by searching for the least sum-squared error in the difference between the predicted and experiment signals across the entire T_{SR} range.

Results: Figure 2 shows the simulation results of the magnetization signal with the two-phase spin model using global SR-T_1^{app} measurement over 12 seconds (a) and the expanded period of initial 1 second (b). Basically, spins relax with the same rate of T_1^{app} during Phase 1 and Phase 2, but with a slightly different steady state level. Spins in Phase 2 have relatively higher signal intensity because those flowing spins are fully relaxed instead of being saturated as the spins during Phase 1. In addition, spin magnetization recovers slightly faster in Phase 1 than Phase 2 (not shown in the currently present figures) since the recovery of arterial magnetization M_a is negligible in Phase 1. The mean transit time under normocapnia condition was 280±16 ms (Mean±SE, n=20); and it shortened to 218±10 ms when CBF or blood velocity increased under mild hypercapnia condition. Moreover, the transit time result was reproducible within an individual rat, for example, the calculated transit time all appeared at 310 ms under normocapnia and it declined to a range of 170-210 ms under four occurrences of hypercapnia in one rat. Figure 3 shows the transit time determination with a 0.5-cm slab saturation preparation (Fig. 3a) and global SR (Fig. 3b) in a representative rat.

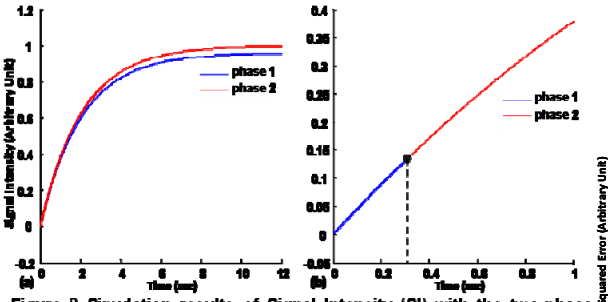


Figure 2 Simulation results of Signal Intensity (SI) with the two-phase spins model using Eq.3-5. (a) SI relaxation of spins of both phase1 and 2 over 12 seconds. (b) Theoretical SI relaxation of spins within initial 1 second according to the two-phase spins model. The junction point corresponds to the transit time. Simulation parameters: $R_1^{app} = 0.4833\ s^{-1}$; $R_1^{int} = 0.4642\ s^{-1}$; $t_{tran} = 0.3s$; $M_b^0 = 1$.

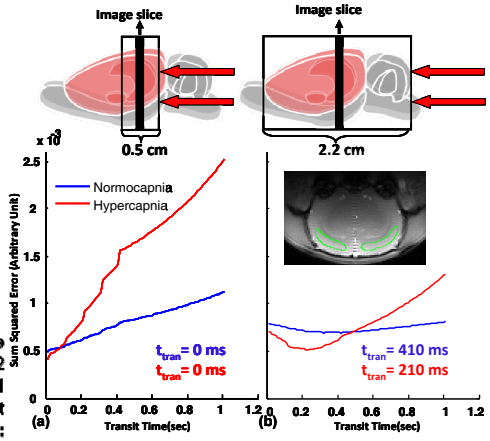


Figure 3 (a) Transit time fitting result of 0.5cm slab saturation band T_1^{app} measurement using two-phase spins model in a representative rat. (b) Transit time fitting result of global SR-T_1^{app} measurement in the same rat. Data from ROI in the brain somatosensory cortex indicated within the green line are used.

Discussion and Conclusion: The junction point between Phase 1 and Phase 2 as proposed in the two-phase spin model is the key to determine the blood transit time in the rat brain. It represents a boundary condition in time domain of the spins being perturbed (SR in the present case) and unperturbed, thus, the spins relax with different dynamics during the two phases. Our results show great consistency and reproducibility for determining the transit time and the results are coincident with the reported transit times under both normacapnia and hypercapnia conditions in the rat brain[1-5]. When the thickness of saturation slab was reduced to 0.5 cm, the uncertainty for determining the transit time became large as illustrated by Fig. 3a. This observation is not surprising since the transit time in this case becomes substantially short, resulting less power for performing regression since only one or two T_{SR} points (i.e. 0.008 and 0.1sec) were acquired in our experiment. On the other hand, this result indirectly confirmed the validity of the two-phase spin model. A potential error of T_1^{app} fitting could result from the fact that there is a slight difference of the modulus of spins between two phases (see Eqs. 3 and 4), however, it is expected to be subtle as demonstrated in the present study.

In conclusion, the SR-T_1^{app} method provides a simple and unique tool for noninvasively and simultaneously imaging rat brain absolute CBF, CBF change[7-8], and blood transit time under physiology and pathology conditions. **Acknowledgments:** NIH grants: NS41262, NS57560, P41 RR08079 and P30NS057091; and WM Keck foundation. **References**: 1. Detre et al. *MRM*, 1992; 2. Tsekos et al. *MRM* 1998; 3. Zhang et al. *MRM* 1992; 4.*Wengener et al, 2007*; 5. Kim, *JCBFM*, 2007; 6. Dobre et.al. *MRI,* 2007; 7. Wang et.al. *ISMRM proceedings*, 1481, 2009. 8. Wang et.al *ISMRM proceedings*, 1213, 2010.