Dynamic changes of on-resonance T1rho dispersion during global ischemia: a 9.4 T study

T. Jin[1], and S-G. Kim[1]
[1]Neuroimaging laboratory, Department of Radiology, University of Pittsburgh, Pittsburgh, PA, United States

Introduction

The spin-lattice relaxation time in the rotating frame ($T_{1\rho}$) has been reported to be a sensitive indicator of cerebral ischemia and can provide complementary MR information of tissue status to water diffusion and perfusion [1,2]. $T_{1\rho}$ is most sensitive to molecular fluctuations with correlation time close to the inverse of the Rabi frequency of the applied spin-locking (SL) pulse. In biological tissue, previous studies have demonstrated that the chemical exchange between bulk water and labile protons of protein or metabolites is an important contributor for the $T_{1\rho}$ relaxation in the frequency range of below several kHz [3]. The chemical exchange contrast is related to the difference in the Larmor frequencies of the exchanging protons which increases with the magnetic field strength. Thus, to evaluate whether a large $T_{1\rho}$ contrast can be detected at a high magnetic field of 9.4 T and to obtain some insight about the ischemia-induced changes in the tissue microenvironment, we studied the dynamic responses of $T_{1\rho}$ during KCL-induced global ischemia for six different SL frequencies ($\nu_1 = \gamma B_1$).

Methods

All MRI experiments were performed on a 9.4 T magnet. Sprague-Dawley rats (n = 4) were anesthetized under isoflurane and scanned with a surface coil. 6 mg/kg of iron oxide particles were injected to suppress the intravascular signals. All data were obtained from a cortical region of interest where the B_1 field was relatively uniform. A double spin-echo EPI sequence with adiabatic SL preparation was used [4] and the imaging parameters were: field of view = 2.56 × 2.56 cm^2, slice thickness = 4 mm, matrix size = 64 × 64, and TR = 2.5 s. Cardiac arrest was induced by bolus injection of 0.5-1 ml of saturated KCL. To measure the $T_{1\rho}$ and T_2 responses, eight images with different $T_{1\rho}$- and T_2-weighting were acquired sequentially. A control series and a T_2-weighted series were acquired without SL preparation, with TE = 25 ms and 60 ms, respectively. For the six $T_{1\rho}$-weighted series, TE = 25 ms, and the SL preparation has duration of spin-locking (TSL) = 50 ms with ν_1 = 125, 250, 500, 1000, 2000, and 4000 Hz, respectively. For each ν_1, an $R_{1\rho}$ (= $1/T_{1\rho}$) time series was calculated from the control and the $T_{1\rho}$-weighted images, by pixel-wise fitting to a monoexponential decay on TSL. Similarly, an R_2 series was calculated from the control and the T_2-weighted series.

The $T_{1\rho}$ relaxation targets all of the chemical exchange sites of the *in vivo* tissue, including amide, amine, and hydroxyl groups of proteins, peptides, and metabolites, etc. It was recently reported that on-resonance $T_{1\rho}$ is not sensitive to the slow amide-water chemical exchange, but is instead sensitive to the faster amine- and hydroxyl-water proton exchanges [5]. Here we adopted a bi-Lorentzian function to fit our experimental data [6]:

$$R_{1\rho} = R_{2,0} + p \cdot \left[\frac{f \cdot \delta_1^2 \cdot k_1}{\delta_1^2 + \omega_1^2 + k_1^2} + \frac{(1-f) \cdot \delta_2^2 \cdot k_2}{\delta_2^2 + \omega_1^2 + k_2^2} \right], \qquad (1)$$

where $R_{2,0}$ is the transverse relaxation rate of water in absence of chemical exchange, p is the total population of labile non-water protons, $\omega_1 = 2\pi\nu_1$, f and (1-f) is the fraction of hydroxyl and amine protons, respectively, and δ_i and k_i (i=1,2) are the chemical shift and exchange rate between hydroxyl- and amine- and water protons, respectively. For fitting, data of every 2 minutes were averaged to improve the signal to noise ratio, and δ_1 = 1 ppm and δ_2 = 3 ppm were chosen for hydroxyl and amine proton exchanges [7]. To minimize the variation of fitting, p was fitted from the averaged baseline data and kept constant for the whole time period. For simplicity, a restriction of $k_2 = \alpha \cdot k_1$ was applied with a fixed α so that k_1 and k_2 would change proportionally. Our metabolite phantom experiments at room temperature showed that k is on the order of 1000-4500 and ~10^4 s^{-1} for the hydroxyl protons and amine protons, respectively (not shown). Here, α = 8 was used in the fitted results below (for 3 ≤ α ≤ 50, the results were qualitatively similar and showed same trends of changes)

Results and discussions

The baseline $R_{1\rho}$ values showed large dispersion in the ν_1 range of 125 to 4000 Hz (Fig. A). The changes of $R_{1\rho}$, interestingly, were strongly dependent on ν_1 (Fig. B). The temporal responses can roughly be separated into two periods: within ~3 minutes after KCL injection, $R_{1\rho}$ decreased for $\nu_1 \geq 2000$ Hz whereas increased for $\nu_1 \leq 1000$ Hz, and R_2 showed large variation. After 3 minutes, all $R_{1\rho}$ curves started to decrease at similar rate, and R_2 also decreased. The largest $R_{1\rho}$ increase appeared for $\nu_1 \approx 250$ Hz instead of 125 Hz, likely because of the residue susceptibility effect contribution to $R_{1\rho}$ measured with a small ν_1. The difference in $R_{1\rho}$ measured with ν_1 = 250 and 4000 Hz, an indication of the $R_{1\rho}$ dispersion, increased rapidly within the initial 3 minutes of ischemia and then remained fairly constant (Fig. C). Fitting to Eq. (1) gave p = 0.0063 ± 0.0004 (n = 4). The fitted k_1 (k_2 as well) decreased ~34% within the first 25 minutes of ischemia (Fig. D), indicating a slow down of exchange mainly due to tissue acidosis. As expected from Eq. (1) the chemical exchange contribution to $R_{1\rho}$ is minimal for large ω_1, the decrease in $R_{2,0}$ is very similar to the time course of $R_{1\rho}$ of ν_1 = 4000 Hz (Fig. E), which may be related to cell swelling and temperature drop. Finally, the change of the relative population of hydroxyl protons may provide some information about the metabolic responses during ischemia (Fig. F).

Our results agreed to a large extent with a previous global ischemia study at 4.7 T by Kettunen et al. [2]. They observed that $T_{1\rho}$ increased ($R_{1\rho}$ decreased) ~30% for B_1 = 1.6G (~6700 Hz) but did not change for B_1 = 0.2 G (~850 Hz). From our data at 9.4 T, the $R_{1\rho}$ showed opposite changes for large and small ν_1 values, and the change would be minimal for 1000Hz < ν_1 < 2000Hz. In summary, we confirmed that $T_{1\rho}$ at 9.4 T is a fast and sensitive indicator of ischemia. Compared with the amide-proton transfer approach which can also probe the ischemic tissue acidosis [7], $T_{1\rho}$ dispersion may provide complementary information about the ischemic tissue changes and similar or enhanced sensitivity, due to its sensitivity to faster amine- and hydroxyl-proton exchanges.

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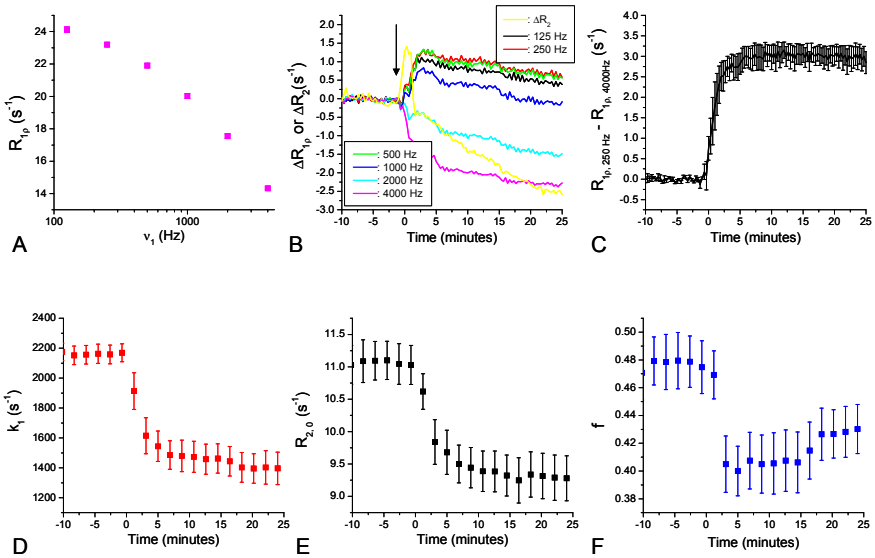

Fig. 1 The baseline $R_{1\rho}$ dispersion (A), and the dynamic $R_{1\rho}$ and R_2 changes (B) during global ischemia induced by KCL injection. The arrow indicates time of injection. (C). The dynamic $R_{1\rho}$ dispersion between ν_1 = 250 and 4000 Hz increased during global ischemia. The hydroxyl-water proton exchange rate (D), $R_{2,0}$ (E), and the relative population of hydroxyl-protons (F), all decreased during ischemia. Error bars: the standard error of the mean.