Dynamic changes in the tissue microenvironment induced by hypercapnia and hyperoxia: a T1rho dispersion study at 9.4 T

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 applied in many pathological studies, including cartilage degradation, cerebral ischemia, and neurodegeneration diseases. Recently, it has also been reported that the $T_{1\rho}$ contrast can detect dynamic changes in the tissue microenvironment induced by hypercapnia [1], hyperoxia challenges [2], or neuronal activation [3]. $T_{1\rho}$ is most sensitive to molecular fluctuations with correlation times close to the inverse of Rabi frequency of the applied spin-locking (SL) pulse. Thus, the $T_{1\rho}$ relaxation time, measured with different SL frequencies ($\nu_{1,SL} = \gamma B_{1,SL}$), which is termed $T_{1\rho}$ dispersion, provides valuable information about the underlying physiological mechanisms. Previous studies have demonstrated that the chemical exchange between labile protons of proteins and the bulk water may be an important contributor to $T_{1\rho}$ dispersion in biological tissues in the low-frequency range of below several kHz [4]. In order to gain more insight about the underlying mechanisms of dynamic $T_{1\rho}$ changes, we investigated the $T_{1\rho}$ response during hypercapnia and hyperoxia for two different SL frequencies.

Methods

All MRI experiments were performed on a 9.4-T magnet. Sprague-Dawley rats were anesthetized under 1.3-1.5% isoflurane and scanned with a 1.7-cm diameter surface coil. Iron oxide particles (4-5 mg/kg) were injected initially to suppress the intravascular signals. In dynamic susceptibility change experiments (n = 4), two doses of 1 mg/kg iron oxide particles were injected in a 13-minute run. Two types of gas challenge were studied: inhalation of 8% CO_2 for 6 minutes (n = 5) or 60% O_2 for 3 minutes (n = 4). A double spin-echo sequence with an adiabatic SL preparation was used [5], and the imaging parameters were matrix size = 64 × 64 and TR = 2 s. For dynamic susceptibility experiments and hypercapnia experiments, the field of view was 2 × 2 cm^2, slice thickness was 2 mm and TE was 25 ms. For hyperoxia experiments the field of view = 2.56 × 2.56 cm^2, slice thickness = 4mm, and TE = 15 ms. In each run, three images with different $T_{1\rho}$ weightings were acquired sequentially, which had a duration of spin-locking (TSL) = 0, TSL = 50 ms with $\nu_{1,SL}$ = 500 Hz, and TSL = 50 ms with $\nu_{1,SL}$ = 2000 Hz, respectively. For each SL frequency, an $R_{1\rho}$ (= $1/T_{1\rho}$) image (Fig. 1C) was calculated from the images without (Fig. 1A) and with 50-ms SL preparation (Fig. 1B), by pixel-wise fitting to a monoexponential decay on TSL. The data with TSL = 0 represent the spin-echo BOLD response, and an R_2 change was calculated. Thus, three time courses were generated.

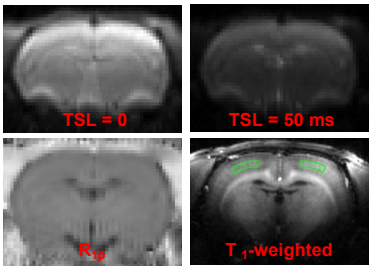

Fig. 1 Baseline spin-echo EPI image (A), $T_{1\rho}$-weighted image (B), and the calculated $R_{1\rho}$ map (C). (D) The green cortical regions of interest on the $T_{1\rho}$-weighted image were selected for data analysis.

Results and discussions

Our first experiment was to examine whether an increase in the intravascular susceptibility effect could cause any significant change in tissue $R_{1\rho}$. Fig. 2A shows that the two iron oxide injections led to a 1.6 s^{-1} increase for R_2, whereas the change in $R_{1\rho}$ was more than one order of magnitude smaller, especially for $\nu_{1,SL}$ = 2000 Hz, which is almost independent of the susceptibility change. The increase of $R_{1\rho}$ at $\nu_{1,SL}$ = 500 Hz (0.05 s^{-1}) was only ~3.0% compared to that of R_2. At 4.7 T and with a $\nu_{1,SL}$ field of ~2500Hz, Kettunen et al. observed a 1.8 ms increase of $T_{1\rho}$ (decrease in $R_{1\rho}$) during severe hypercapnia and a 0.3 ms increase during mild hypercapnia. Interestingly, our $T_{1\rho}$ data with the two SL fields illustrate an opposite direction of $T_{1\rho}$ changes for 500 Hz vs. 2000 Hz. The tissue $R_{1\rho}$ increased for an SL frequency of 500 Hz but decreased slightly for $\nu_{1,SL}$ = 2000 Hz (Fig. 2B). The temporal changes of $R_{1\rho}$ followed the stimulation closely (yellow shaded area). Since the change in R_2 was very small (because of the competition of the BOLD and CBV increase with 5 mg/kg intravascular iron oxide), the observed change in $R_{1\rho}$ dispersion should represent changes in tissue microenvironment without contamination from vascular susceptibility variations. During hyperoxia, the change in $R_{1\rho}$ was much smaller as compared to hypercapnia. The prominent change in R_2 (-1.5 s^{-1}) indicated that there should be a considerable contribution of susceptibility effect to the observed $\Delta R_{1\rho}$ of -0.06 s^{-1} at $\nu_{1,SL}$ = 500 Hz. Thus, at 9.4 T, $T_{1\rho}$ appears to be insensitive to the oxygenation state of the tissue, which disagrees with a previous report in human at 1.5 T [2] but agrees with a previous rat study at 4.7 T [1].

Since chemical exchange is the important contributor for the $T_{1\rho}$ dispersion [4] and the $R_{1\rho}$ change during hypercapnia likely reflects a reduction in pH or the exchange rate k, the positive and negative changes of $R_{1\rho}$ can provide some insights into the underlying chemical exchange process. The chemical exchange contrast is dependent on the chemical shift δ and the exchange rate k between the water and the labile proton from proteins and/or metabolites. For tissues *in vivo*, many different exchangeable protons with a wide range of δ and k contribute to the on-resonance $R_{1\rho}$. For simplicity, assuming a two-site exchange, the exchange contribution to $R_{1\rho}$ satisfies $R_{ex} \sim k/(\delta^2 + \omega_{1,SL}^2 + k^2)$ [6], where $\omega_{1,SL} = \nu_{1,SL}/2\pi$. The derivative of R_{ex} with respect to k goes to zero when $\delta^2 + \omega_{1,SL}^2 = k^2$ or $\omega_{1,SL} = (k^2 - \delta^2)^{1/2}$. The opposite change of $R_{1\rho}$ at $\nu_{1,SL}$ = 500 Hz and 2000 Hz suggests that $(k^2-\delta^2)^{1/2}$ is likely between these two frequencies. With $(k^2-\delta^2)^{1/2}$ > 500 Hz, our results further suggest that the effective chemical exchange measured with on-resonance $T_{1\rho}$ at 9.4 T is in the intermediate or intermediate to fast exchange regime (k/δ>1).

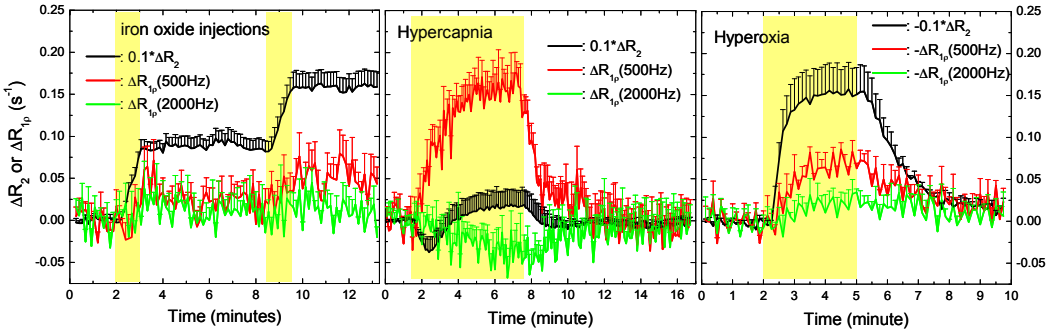

Fig. 2 Time courses of the R_2 and $R_{1\rho}$ changes during two iron oxide injections (A), 6 minutes of hypercapnia challenge (B), and 3 minutes of hyperoxia (C). The yellow shaded areas indicate periods of injection or gas challenge. For easy display and comparison, the changes in R_2 were scaled down 10 times, and the changes during hyperoxia were inverted.

Acknowledgments: This work is supported by NIH grants EB008717, EB003324, EB003375, and NS44589.

References:

[1]. Kettunen MI et al, *MRM* 48:470 (2002). [2]. Tailor DR et al., *PISMRM* 17:4527 (2009). [3]. Jin T et al., *PISMRM* 17:1577 (2009). [4]. Duvvuri U et al., *PNAS* 98:12479 (2001). [5]. Jin T et al., *NeuroImage* 51:1378 (2010). [6]. Trott O et al., *JMR* 154 :157 (2002).