T1rho measurement in rat brain tissue changes associated with aging and chronic hypertension

Feng ZHAO[1], Li-Hong Zhang[2], Jing Yuan[1], Queenie Chan[3], David Yew[2], and Yi-Xiang Wang[1]

[1]*Department of Imaging and Interventional Radiology, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong,* [2]*Brain Research Centre, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong,* [3]*Philips Healthcare, Hong Kong, Hong Kong*

Introduction: T1rho represents the spin lattice relaxation time constant in the rotating frame, which determines the decay of the transverse magnetization in the presence of a "spin-lock" radiofrequency field. T1rho relaxation has been suggested as a sensitive biomarker to detect early stage of intervertebral disk degeneration [1], cartilage degeneration in osteoarthritis [2], and liver fibrosis [3]. In neuroimaging, T1rho MR has been used to study Alzheimer' disease in mouse model [4], as well as Alzheimer' disease, mild cognitive impairment and Parkinson's disease in patients [5,6]. Aging and hypertension are the common risk factors for neurodegenerative disease [7]. Spontaneously hypertensive rats (SHR) are normotensive at birth and gradually develop severe hypertension in the first 2-4 months of life. At 6 months they develop a sustained hypertension compared to their normotensive control strain, the Wistar Kyoto (WKY) rats. Recently, we reported that at the age of 6 months, T1rho relaxation time was higher in regions of thalamus, hippocampus and cortices in SHR rats compared with those of age matched WKY rats [8]. In the current study, we longitudinally followed up these groups of rats at 9 months and 12 months.

Material and Methods: Eleven male SHR and eleven male WKY control rats were used in the study with the animal ethics approval. The rats were MR scanned longitudinally at the age of 6-month, 9-month, and 12-month. MRI was performed on a 3 T clinical scanner (Achieva, Philips Healthcare, Best, The Netherlands). After anesthesia, animals were positioned prone and a custom made quadrature volume RF coil of 7cm internal diameter was used as signal transmitter and receiver. 14 axial slices were used to cover the whole rat brain. For T1rho measurement, a rotary echo spin-lock pulse was implemented in a 3D fast field echo (FFE) sequence. Spin-lock frequency was set as 500 Hz and images were acquired at spin-lock times (TSLs) of 1 ms, 20 ms, 50ms, and 80 ms, TE and TR were 3.6 ms and 7.4 ms respectively. TI (delay time) after acquisition was set as 5500 ms to restore equilibrium magnetization prior to the next T1rho preparation. The voxel size was 0.3×0.35×1.50 mm3. The flip angle was 40 degree and the number of signal average was 4. T1rho maps were computed on a pixel-by-pixel basis using a mono-exponential decay model of $M(TSL)=M_0*\exp^{(-TSL/T1rho)}$ with a home-made Matlab program (Mathworks, Natick, MA, USA). T1rho values were measured by user-defined regions of interest (ROIs) in the bilateral thalamus (T), hippocampus (H), and cortices (C) from T1rho maps (Fig.1). Data are presented as mean ± standard deviation. All statistical analyses were done using SPSS 14.0 (SPSS, Chicago, IL). The Mann-Whitney U test was used for non-paired comparison.

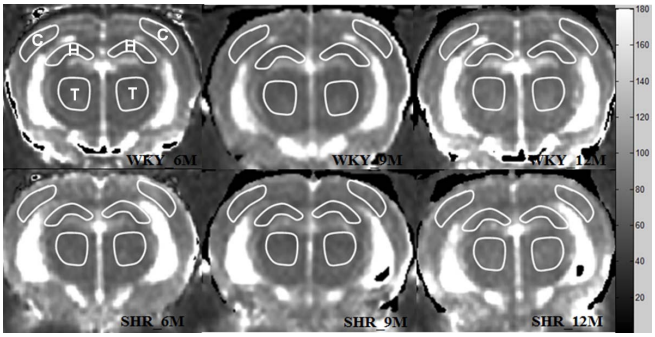
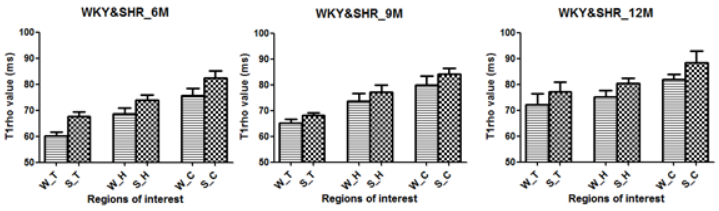


Fig. 1*. T1rho maps for one WKY rat (above) and one SHR (below) at the age of 6-month (left), 9-month (middle), and 12-month (right). User defined ROIs are placed on bilateral thalamus (T), hippocampus (H) and cortices (C).*

Table. 1. *T1rho values in the thalamus, hippocampus and cortices of normotensive Wistar-Kyoto (WKY) rats and spontaneously hypertensive rats (SHR) at different ages. Diff%=(measurement of SHR- measurement of WKY)/ measurement of WKY. a: p<0.05 vs. age-matched WKY rats. b: p value for trend <0.001 in brain region of WKY and SHR groups with aging process.*

	6 months			9 months			12 months		
	WKY	**SHR**	**Diff%**	**WKY**	**SHR**	**Diff%**	**WKY**	**SHR**	**Diff%**
thalamus (ms)	60.1±1.5	67.6±1.7 [a]	12.6%	65.1±1.7	68.2±1.1 [a]	4.7%	72.0±4.3 [b]	77.1±3.8 [a b]	7.0%
hippocampus(ms)	68.6±2.4	73.9±2.1 [a]	7.7%	73.6±3.0	77.1±2.7 [a]	4.7%	75.1±2.6 [b]	80.3±2.1 [a b]	7.0%
cortices (ms)	75.6±2.9	82.3±2.8 [a]	8.9%	79.9±3.6	84.1±2.5 [a]	5.2%	82.0±2.0 [b]	88.5±4.4 [a b]	7.9%

Fig.2 *T1rho values in thalamus (T), hippocampus (H) and cortices (C) of WKY (W) rats and SHR (S) at age of 6-month(left), 9-momth (middle), and 12-month (right).*



Results: The data of one WKY rat at age of 6-month, 2 WKY rats at age of 9-month, 1 SHR at age of 9-month and 2 SHR at age of 12-month were not included in this study due to imaging artifacts. Satisfactory T1rho images and T1rho maps were obtained for all the remaining animals. Typical T1rho maps of SHR and WKY rat brain at different time phase are shown in Fig.1. T1rho values in thalamus, hippocampus and cortices of hypertensive rats were consistently higher than those of WKY control rats at the age of 6-month, 9-month and 12-month. At the age of 6-month, T1rho values in thalamus, hippocampus and cortices of SHR were 12.6% ($p<0.05$), 7.7% ($p<0.05$), and 8.9% ($p<0.05$) higher than WKY rats (Table1, Fig.2). At the age of 9-month, T1rho values in thalamus, hippocampus and cortices of SHR were 4.7% ($p<0.05$), 4.7% ($p<0.05$), and 5.2% ($p<0.05$) higher than WKY rats (Table1, Fig.2). At the age of 12-month, T1rho values in thalamus, hippocampus and cortices of SHR were 7.0% ($p<0.05$), 7.0% ($p<0.05$), and 7.9% ($p<0.05$) higher than WKY rats (Table1, Fig.2). The regional brain T1rho values of both SHR and WKY rats increased with aging process. Compared to the measurement at 6-month, the T1rho values in thalamus, hippocampus and cortices in SHR at age of 12-month were increased by 14.1%, 8.7% and 7.5 respectively. Similarly, at 12-month the increase of T1rho values in thalamus, hippocampus and cortices of WKY rat brains were 20.0%, 9.5% and 8.5%, respectively. The p-value for trend was <0.001 in each brain regions of WKY and SHR groups during aging process (Table 1). Meanwhile, the percentage regional T1rho difference between SHR and WKY rats did not increase with aging process (Table1).

Discussion: Aging and hypertension are two major risk factors for common neurodegenerative diseases, including Alzheimer's disease, and Parkinson's disease [7]. With aging process, decrease of cerebral blood flow (CBF) [9], dysfunction of blood brain barrier [10, 11], occurrence of brain atrophy [12], loss of nerve cells [11, 13] commonly exhibited in the brain of aged rats. The hypertensive rats exhibit these similar changes [9-12, 14], but they can be more advanced than the age-matched normotensive rats. Haris et al suggested that the increased T1rho in Parkinson's disease patients with dementia may be associated with the increased atrophy and Alzheimer' disease related changes [6]. In this study, the rat brain changes associated with aging and hypertension both contributed to increase of T1rho values in the thalamus, hippocampus and cortices regions. This study further suggested T1rho MR can be a potential technique to monitor brain tissue alterations due to aging process and chronic hypertension.

References: *[1] Nguyen AM, et al. J Bone Joint Surg Am.2008; 90(4):796-802. [2] Burstein D, et al. Radiol Clin North Am. 2009; 47(4):675-86. [3]Wang YX, et al. Radiology. 2011;259(3):712-9. [4] Borthakur A, et al, J Mag Res Imaging. 2006;24(5):1011-7. [5] Haris M, et al, JMRI. 2009;29(5):1008-12. [6] Haris M, et al, J Neurol. 2011; 258(3):380-5. [7] J. Sandhya et al. International Journal of Engineering and Technology, 2010; vol.2, no. 4. [8]Zhao F, et al, ISMRM 2012;0347. [9]Lee, T.H., et al. Exp Neurol, 2011. 227(2): 314-21. [10]Knox, C.A., et al. Acta Neuropathol, 1980. 51(1): 1-13. [11]Tomassoni, D. et al. Brain Res, 2010. 1325: 155-63. [12]Amenta F, et al. Ital J Anat Embryol.2010;115(1-2):13-7.[13]Napoleone, P., et al. Arch Gerontol Geriatr, 1990. 10(2): 173-85. [14]Mignini, F., et al. Clin Exp Hypertens, 2004. 26(4): 287-303.*