34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

Effect of Gadobutrol on VX2 Magnetic Resonance Diffusion-Weighted Imaging

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Abstract—**The aim of this study was to evaluate the effect of contrast agent gadobutrol on the magnetic resonance diffusion-weighted imaging (MR DWI). Gadobutrol has higher relaxivity than Gd-DTPA and it also has higher formulation 1.0 M than Gd-DTPA 0.5 M. VX2 tumor implanted on the left thigh of each New Zealand rabbit was used as the animal model. The MR scanning was performed using a 1.5 T clinical whole-body MR scanner with an 8-channel knee coil. The results showed that there were significant differences in the signal-to-noise ratio (SNR) and apparent diffusion coefficient (ADC) values between tumor and muscle both before and after gadobutrol injection (0.1 mmol/kg). However, there were no significant differences in the SNR and ADC values of tumor or muscle before and after gadobutol administration. There were also no significant difference in the contrast-to-noise ratio (CNR) values of tumor and muscle before and after gadobutrol injection.**

I. Introduction

Magnetic resonance imaging (MRI) has grown very rapidly. It has the advantage of high contrast between soft tissues. Besides, it has no radiation. Therefore, it is very suitable for lesion detection and therapy follow-up. MRI also provides many parameters showing the characteristics of tissues. Some parameters may have potential to distinguish tumor from normal tissues and be used as biomarkers in clinic. Many studies on magnetic resonance diffusion weighted imaging (DWI) have been performed to see if it can be used for tumor diagnosis and therapy monitoring. Diffusion is a kind of thermally induced random motion. The protons inside tissues always have diffusion phenomenon once there is temperature. Apparent diffusion coefficient (ADC) can be calculated from two DWI signals, one with and the other without diffusion weighted gradients. In the beginning, ADC was applied in brain imaging, especially in the early detection of stroke. It is also widely applied on oncology now. Cancer usually has lower ADC value than normal tissues because it has higher cell density. Because ADC value can present some information about the microstructures of tissues, it has potential to be a biomarker for tumor detection and therapy follow-up [1-7].

MR DWI is usually performed without or before contrast agent injection. In some situations, it may be necessary to acquire MR DWI after contrast agent injection. The effects of intravenous Gd-DTPA on MR DWI have been investigated in brain, liver, prostate and kidney [2-7]. Gd-DTPA is the first commercial contrast agent obtaining FDA approval in 1988 and popularly used in clinic. After injection, it distributes in the vessel first, and then transport to interstitial system, and finally excretes from the kidney system. Gadobutrol is another commercial contrast agent. It was first applied in angiography because of its higher formation 1.0 M than Gd-DTPA 0.5 M, which can provide sharper appearance of vessels. Because of its higher relaxivity than Gd-DTPA, it has also been applied on oncology. It may produce higher and longer enhancement than Gd-DTPA [8, 9]. If the DWI signal changes because of the relaxation and susceptibility effects of gadobutrol needs to be investigated. As we know, there is no report about the effect of gadobutrol on the DWI of tumors. This study was to investigate if there were any significant changes of DWI signals at 30 minutes after gadobutrol injection and see if it was acceptable to have ADC measurements after contrast agent injection. A VX2 animal model was used in this study [1, 9].

II. Materials and Methods

A. MR scanning

All the MRI studies were performed on a 1.5 T whole-body MR scanner (Signal HDxt, GE Medical Systems, Milwaukee, WI) with an 8-channel knee coil. The protocol of the animal study was approved by our institutional review board. Ten rabbits were prepared for MRI scanning. The VX2 tumor was implanted on the left thigh of each rabbit. The rabbit was anesthetized with 16 mg/kg Zoletil 50 and 14 mg/kg Rompun 2%. Before MRI scanning, a butterfly needle with gauge 23 was inserted into an ear vein for later gadobutrol injection. The rabbit thighs were put into the knee coil with the left thigh up and the VX2 mass was placed in the center. A water phantom was put aside for the reference. After a 3-plane localizer scan, spin echo - echo planar imaging (SE-EPI) was performed for DWI with the following parameters: field of view (FOV) = 16 × 16 cm^2, matrix size (MS) = 128 × 128, slice thickness (ST) = 5 mm, gap = 2.5 mm bandwidth (BW) = 250 kHz, number of excitation (NEX) = 2, TE = 92.4 ms, and TR = 4000 ms. The b value, a constant depending on the amplitude and duration of the

*Research supported by National Science Council of Taiwan (99-2221-E-214-008).

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diffusion-weighted gradient was 0 or 1000 s/mm^2. It took 36 seconds to complete the scanning of DWI. Then 2-dimentional fast spoiled recalled gradient echo (2D FSPGR) pulse sequence was performed for dynamic contrast enhanced MRI (DCE-MRI). The scanning parameters for DCE-MRI were TR = 100 ms, TE = 1.3 ms, FA = 60^o, BW = 31.3 kHz, ST = 5 mm, gap = 2.5 mm, NEX = 1. The scan time for each image was 14 s. Four pre-contrast images were acquired first. Then, 0.1 ml/kg gadobutrol (Gadovist, Schering, Berlin, Germany) was bolus injected through the ear vein and flushed with 1 ml saline. The total scan time for DCE-MRI was 30 min followed by another DWI with the same parameters mentioned above. All acquired MR images were transferred to an Advantage Window workstation for image analysis.

B. Data analysis

Several regions of interest (ROIs) were chosen from muscle and the peripheral regions of tumor. SNR was calculated as follows:

$$SNR_{T,M} = S_{T,M}/STD_{BG}, \quad (1)$$

where T indicates tumor, M indicates muscle, $S_{T,M}$ is the MR signal of tumor or muscle, and STD_{BG} is the standard deviation of background in DWI with b = 1000 s/mm^2. CNR was calculated as follows:

$$CNR = SNR_T - SNR_M, \quad (2)$$

Apparent diffusion coefficient (ADC) was calculated according to the following equation:

$$ADC_{T,M} = (1/b)\ln(S_{0T,M}/S_{T,M}), \quad (3)$$

where $S_{T,M}$ and $S_{0T,M}$ are the MR signals of tumor or muscle obtained with and without DW gradients, respectively. Here, the b value is 1000 s/mm^2. Student's t-test was used for the statistical analysis of SNR and ADC values between the tumor and muscle. It was also used to compare the SNR_T, SNR_N, CNR, ADC_T, and ADC_M values before and after gadobutrol injection. It was considered significantly different while $p < 0.05$.

III. Results

Figure 1 and 3 show the DW images obtained before and after gadobutrol injection. Figure 1(b) and 3(b) show the T_2 images acquired without DW gradient, i.e. b = 0. Figure 1(a) and 3(a) show the DW images acquired with the same amplitude and duration of DW gradient, i.e. b =1000 s/mm^2. T_2 images had larger signal than DW images. Both DW and T_2 images obtained after gadobutrol injection had no obvious difference from those obtained before gadobutrol injection. Figure 2 shows the DCE-MRI before and at 30 minutes after gadobutrol injection. The rim of the tumor had higher enhancement than the center of tumor and muscle. Figure 4 shows the SNR values of VX2 tumor and muscle on DWI before and after gadobutrol injection. The SNR values of VX2 and muscle before gadobutrol injection were 533 ± 298 and 82.2 ± 40.9, respectively. The SNR values of VX2 and muscle after gadobutrol injection were 525 ± 339 and 80.2 ± 49.2, respectively. The SNR values of VX2 tumor were larger than those of muscle. There were significant differences of the SNR values between VX2 tumor and muscle both before and after gadobutrol injection ($p < 0.05$). However, there was no significant difference in the SNR values for VX2 tumor before and after gadobutrol injection ($p = 0.38$), nor for muscle ($p = 0.26$). Figure 5 shows the CNR values between VX2 tumor and muscle before and after gadobutrol injection. The CNR values before and after gadobutrol injection were 450 ± 268 and 445 ± 300, respectively. There was no significant difference in the CNR values before and after gadobutrol injection ($p = 0.48$). Figure 6 shows the ADC values of VX2 tumor and muscle before and after gadobutrol injection. The ADC values of VX2 and muscle before gadobutrol injection were $(1.17 \pm 0.30) \times 10^{-3}$ mm^2/s and $(1.44 \pm 0.12) \times 10^{-3}$ mm^2/s , respectively. The ADC values of VX2 and muscle after gadobutrol injection were $(1.19 \pm 0.32) \times 10^{-3}$ mm^2/s and $(1.41 \pm 0.12) \times 10^{-3}$ mm^2/s, respectively. The ADC values of VX2 tumor were lower than those of muscle. There were significant differences in the ADC values between VX2 tumor and muscle no matter before or after gadobutrol injection ($p < 0.05$). However, there was no significant difference in the ADC values for VX2 tumor before and after gadobutrol injection ($p = 0.36$), nor for muscle ($p = 0.23$).

IV. Discussion and Conclusions

Nowadays, both DCE-MRI and MR DWI are widely studied on oncology. Scientists are interested in finding reliable biomarkers from the parameters obtained from DCE-MRI or MR DWI for early detection and treatment monitoring. ADC value is one of the potential biomarker and draws much attention. DWI is usually performed before DCE-MRI because it has no need of contrast agent injection. However, it may need to do DWI after DCE-MRI in some specific situations. Then, the effect of contrast agent on the ADC values becomes an issue to be concerned [2-7].

Gd-based contrast agents are often used in DCE-MRI, which are paramagnetic because of unpaired electrons and can reduce the T_1 and T_2 relaxation times of the protons in tissues. In T_1 weighted images, the MR signals increase because of shorter T_1. On the contrary, the MR signals decrease due to the shorter T_2. The contrast agents also cause protons out-of-phase due to susceptibility effects and make MR signals smaller. The effects of relaxation and susceptibility depend on the concentration and relaxivity values of contrast agents. The higher concentration and relaxivity values are, the more serious effects are. Gd-DTPA is the first contrast agent used in clinic in 1988. Since then, several novel contrast agents have emerged for different purposes. Gadobutrol is the first contrast agent with higher formation 1.0 M, which can be used in less volume and make sharper appearance of angiography. It also has higher relaxivity than Gd-DTPA and can produce higher contrast-to-noise ratios in DCE-MRI [8, 9]. The effect of intravenous Gd-DTPA on DWI of brain, liver, prostate and kidney has been investigated [2-7]. However, the impact of gadobutral on DWI has not been reported yet.

In this study, we used the VX2 animal model to investigate the effect of intravenous gadobutrol on the ADC values of tumor and muscle. The VX2 is hypervascular and suitable for MRI studies using clinical MR scanners [1, 9]. The result showed that there were significant differences in SNR and ADC values between tumor and muscle both before and after

gadobutral injection. The tumor has smaller ADC values because it has higher cell intensity so that the diffusion of protons is limited. The result also showed that there were no significant differences of the SNR and ADC values before and at 30 minutes after gadobutrol injection for both tumor and muscle. Also, the CNR values of tumor and muscle were not significantly different before and at 30 minutes after gadobutrol injection. The effect of contrast agents on the ADC values depend on the concentrations of contrast agents in tissues. In this study, the dosage of gadobutrol was 0.1 mmol/kg and the time to measure ADC values after gadobutrol injection was 30 minutes. To measure ADC values with different gadobutrol dosage and at different time after gadobutrol injection needs further investigation. In conclusion, it is acceptable to obtain ADC values of VX2 tumor and muscle at 30 minutes after 0.1 mmol/kg gadobutrol injection.

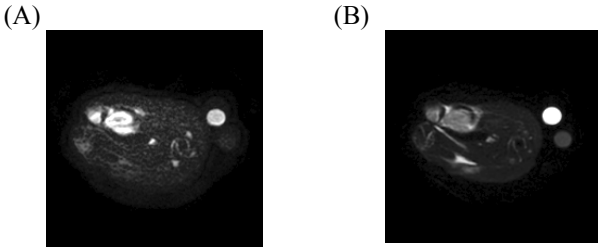

Figure 1. (A) DWI image with b = 1000 s/mm^2 and (B) T_2 image with b = 0 before gadobutrol injection.

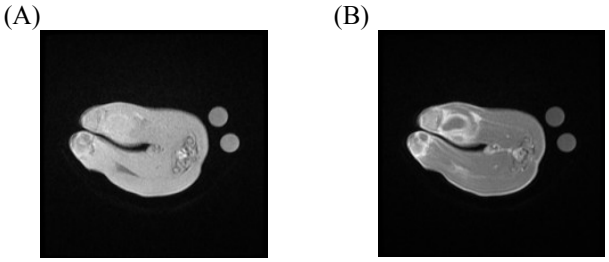

Figure 2. T_1 weighted images (A) before and (B) at 30 min after gadobutrol injection.

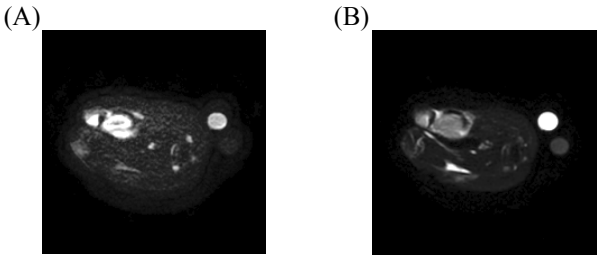

Figure 3. (A) DWI image with b = 1000 s/mm^2 and (B) T_2 image with b = 0 after gadobutrol injection.

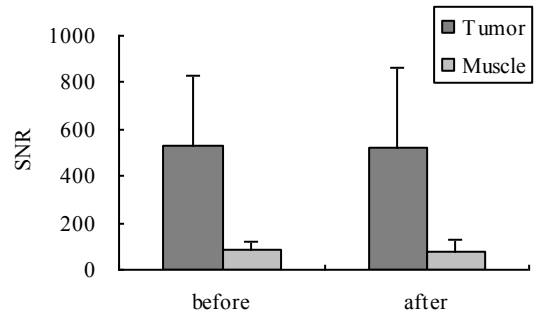

Figure 4. SNR values of VX2 tumor and muscle before and at 30 min after gadobutrol injection.

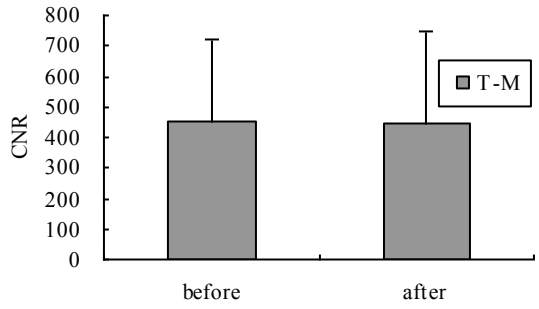

Figure 5. CNR values between VX2 tumor and muscle before and at 30 min after gadobutrol injection.

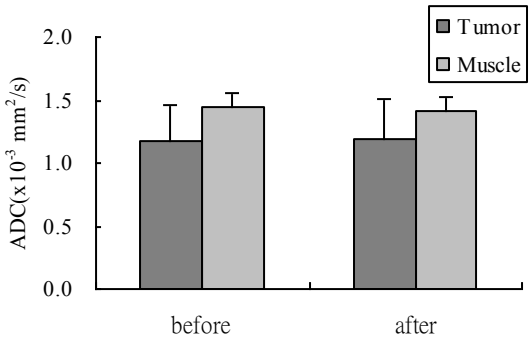

Figure 6. ADC values of VX2 tumor and muscle before and at 30 min after gadobutrol injection.

REFERENCES

[1] H. Shao, Y. Ni, X. Dai, et al. "Diffusion-Weighted MR Imaging Allows Monitoring the Effect of Combretastatin A4 Phosphate on Rabbit Implanted VX2 Tumor Model: 12-Day Dynamic Results," *Eur. J. Radiol.* vol. 81, no. 3, pp. 578-583, Mar. 2012.

[2] K. Yamada, H. Kubota, O.Kizu et al. "Effect of intravenous gadolinium-DTPA on diffusion-weighted images: evaluation of normal brain and infarcts," *Stroke*, vol. 33, no. 7, pp. 1799-802, Jul. 2002.

[3] F.-Y. Chiu, J.-C. Jao, C.-Y. Chen et al. “Effect of intravenous gadolinium-DTPA on diffusion-weighted magnetic resonance images for evaluation of focal hepatic lesions,” *J. Comput. Assist. Tomogr.* vol. 29, no. 2, pp. 176-80, Mar-Apr. 2005.

[4] C Fitzek; H J Mentzel; S Fitzek; D Sauner; W A Kaiser; J R Reichenbach, “Echoplanar diffusion-weighted MRI with intravenous gadolinium-DTPA,”. *Neuroradiology*, Vol. 45, no. 9, pp. 592-7, Sep. 2003.

[5] X. Liu, L. Zhou, W. Peng, M. Qian, “Effect of intravenous gadolinium-DTPA on diffusion-weighted imaging for prostate lesions and normal tissue at 3.0-Tesla magnetic resonance imaging.,” *Acta. Radiol.* Vol. 52, no. 5, pp. 575-80, Jun. 2011.

[6] G. Chen, S.N. Jespersen, M. Pedersen, Q. Pang, M.R. Horsman, H. Stødkilde-Jørgensen, “Intravenous administration of Gd-DTPA prior to DWI does not affect the apparent diffusion constant,” *Magn. Reson. Imaging,* vol. 23, no. 5, pp. 685-689, Jun. 2005.

[7] F. Saremi, S. Sefidbakht, L. Quane, J. Santa Maria, A. Khararjian, M. Jalili, “Effect of intravenous extracellular gadolinium based contrast medium on renal diffusion weighted images,” *Acad. Radiol.* vol. 18, no. 2, pp. 174-183, Feb. 2011.

[8] M. Voth, S. Haneder, K. Huck, A. Gutfleisch, SO. Schönberg, H.J. Michaely, “Peripheral magnetic resonance angiography with continuous table movement in combination with high spatial and temporal resolution time-resolved MRA With a total single dose (0.1 mmol/kg) of gadobutrol at 3.0 T,” *Invest. Radiol.* vol. 44, no. 9, pp. 627-33, Sep. 2009.

[9] JM. Chang, W.K. Moon, JH Cha, et al. “Dynamic contrast-enhanced magnetic resonance imaging evaluation of VX2 carcinoma in a rabbit model: comparison of 1.0-M gadobutrol and 0.5-M gadopentetate dimeglumine,” *Invest. Radiol.* vol. 45, no. 10, pp. 655-61, Oct. 2010.