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Characterizing Amide Proton Transfer Imaging in Hemorrhagic Brain Lesions Using 3T MRI

Ha-Kyu Jeong, PhD^{1,2}, Kyunghwa Han, PhD^{3,4}, Jinyuan Zhou, PhD⁵, Yansong Zhao⁶, Yoon Seong Choi, MD³, Seung-Koo Lee, MD, PhD³, and Sung Soo Ahn, MD, PhD³

¹Philips Korea, Seoul, Korea

²Korea Basic Science Institute, Chungcheongbuk-do, Korea

³Departments of Radiology and Research Institute of Radiological Science, Yonsei University College of Medicine, Seoul, Korea

⁴Yonsei Biomedical Research Institute, Yonsei University College of Medicine, Seoul, Korea

⁵Division of MRI Research, Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States

⁶MR Clinical Science, Philips Healthcare, Cleveland, Ohio, United States

Abstract

Objectives—The aim of this study was to characterize amide proton transfer (APT)-weighted signals in acute and subacute hemorrhagic brain lesions of various underlying aetiologies.

Methods—Twenty-three patients with symptomatic hemorrhagic brain lesions including tumorous (n=16) and non-tumorous lesions (n=7) were evaluated. APT imaging was performed and analyzed with magnetization transfer ratio asymmetry (MTR_{asym}). Regions of interest were defined as the enhancing portion (when present), acute or subacute haemorrhage, and normal-appearing white matter based on anatomical MRI. MTR_{asym} values were compared among groups and components using a linear mixed model.

Results— MTR_{asym} values were 3.68% in acute haemorrhage, 1.6% in subacute haemorrhage, 2.65% in the enhancing portion, and 0.38% in normal white matter. According to the linear mixed model, the distribution of MTR_{asym} values among components was not significantly different between tumour and non-tumour groups. MTR_{asym} in acute haemorrhage was significantly higher than those in the other regions regardless of underlying pathology.

Conclusions—Acute haemorrhages showed high MTR_{asym} regardless of the underlying pathology, whereas subacute haemorrhages showed lower MTR_{asym} than acute haemorrhages. These results can aid in the interpretation of APT imaging in hemorrhagic brain lesions.

Keywords

Cerebral haemorrhage; Magnetic resonance imaging; Amide proton transfer imaging; Magnetization transfer; Brain neoplasms

Introduction

Amide proton transfer (APT) imaging, a subset of chemical exchange saturation transfer (CEST) imaging, utilizes the chemical exchange of amide protons to detect endogenous mobile proteins and peptides at relatively low molecular concentrations without using exogenous contrast agents [1–9]. In APT imaging, exchangeable labile amide protons are saturated by off-resonance radiofrequency (RF) irradiation targeting at the resonance frequency of amide protons at downfield 3.5 ppm with respect to the water resonance. The saturation effect is transferred from amide protons to bulk water protons by a proton exchange mechanism, resulting in MRI contrast which may reveal molecular environments of a tissue [10]. This new MRI technique has been the most widely used form of CEST imaging in clinic, and successfully applied to several diseases in the brain including tumours and cerebral ischemia [5, 11–13]. It has been well known that APT-weighted signals can be affected by various tissue environments, including the concentration of amide and water protons, the exchange rate, and other technical factors used during APT examination [14, 15]. Although the origin of the APT-weighted signal in tumours remains controversial [16, 17], previous studies have shown that APT-weighted signal intensity increases within brain tumours, which has been attributed to increased mobile protein concentrations in tumour cells associated with increased cellular proliferation [4, 5, 7, 11, 18, 19].

Haemorrhages may be associated with various brain pathologies from benign vascular lesions to malignant tumours. The appearance of intracranial haemorrhage (ICH) on MRI is primarily determined by the age of a hematoma. As a hematoma ages, the haemoglobin passes through several forms resulting in characteristic patterns in MRI signal intensities throughout the course of the ICH evolution (hyperacute, acute, early subacute, late subacute, and chronic stages) [20]. This sequential evolution of ICH signal intensity is mainly due to the formation of blood degradation products and their interaction with adjacent water molecules, particularly dipole-dipole interactions and magnetic susceptibility effects leading to proton relaxation [21, 22]. A recent study demonstrated the feasibility of blood as an endogenous CEST agent using a porcine model and human volunteers [23], and another study suggested the possibility of detection and separation of hyperacute ICH and cerebral ischemia using rat models [24]. However, to the best of our knowledge, there have been no studies characterizing APT-weighted image contrast in hemorrhagic brain lesions. Therefore, the aim of this study was to characterize the APT-weighted signal in acute and subacute haemorrhagic brain lesions in patients with and without tumours.

Materials and Methods

Study Population

This retrospective study was approved by the Institutional Review Board and the requirement for informed consent was waived. Twenty-three patients (15 male and 8 female; mean age 52.7 ± 12.8 years) who presented symptomatic ICH were enrolled in this study, and APT imaging was implemented with our routine brain MRI protocols between October 2014 and May 2015. Among the 23 patients, 16 were diagnosed with benign or malignant tumours on histopathology reports (tumour group: metastasis, $n = 9$; glioblastoma, $n = 3$; pituitary adenoma, $n = 2$; hemangioblastoma, $n = 1$; angiosarcoma, $n = 1$) and seven patients were diagnosed with non-tumorous lesions (non-tumour group: cavernous malformation, $n = 6$; post-traumatic haemorrhage, $n = 1$). The primary tumours for the nine metastatic lesions included lung cancer ($n = 6$), melanoma ($n = 1$), cervix cancer ($n = 1$), and spindle cell sarcoma ($n = 1$).

MR Imaging Protocol

MRI studies were performed using a 3.0 T system (Achieva whole-body MR system, Philips Healthcare, Best, The Netherlands) with a 32-channel receive head coil and a whole-body transmit coil. In addition to our standard brain MRI protocols, APT imaging was performed using a three-dimensional (3D) gradient- and spin-echo (GRASE) sequence [25]. APT imaging parameters were as follows: an acquisition voxel size of 2.2×2.2 mm, a slice thickness of 4.4 mm, a repetition time (TR)/echo time (TE) of 3000 ms/17 ms, a turbo spin echo factor of 22; an echo-planar imaging factor of 7 and a total slice of 15 to cover the entire lesions. Six saturation frequency offsets (± 3.0 , ± 3.5 and ± 4.0 ppm) were adapted with four repetitions at ± 3.5 ppm to attain a sufficient signal-to-noise ratio (SNR) within an appropriate clinical time frame [7, 26]. Saturation RF pulses for APT imaging were implemented with an amplitude of 2 μ T and four 200 ms blocks. In addition, main magnetic (B_0) field heterogeneity was measured using water saturation shift referencing (WASSR) technique in a separate scan to account for the sensitivity to water frequency shift induced by B_0 field heterogeneities [27]. WASSR data was obtained using 3D GRASE sequence with 21 offset frequencies ranging from -1.25 ppm (-160 Hz) to 1.25 ppm (160 Hz) at a step of 0.125 ppm (16 Hz), resulting in a full Z-spectrum [28] within the offset frequency range. WASSR data were acquired with a TR/TE of 1250 ms/17 ms and saturation RF pulses with an amplitude of 0.5μ T and two 200 ms blocks, i.e., much lower power and shorter duration than used in APT imaging for estimating water frequency shift from direct water saturation with minimum CEST and magnetization transfer (MT) effects. One reference scan was acquired without saturation RF pulse irradiation. APT and WASSR scans were performed prior to contrast-enhanced T1-weighted MRI acquisition. The total acquisition time for both APT and WASSR scans was 7 min 36 s.

Other conventional MRI images were performed including axial pre-contrast T1-weighted imaging (TR/TE 2000 ms/10 ms, 256×203 matrix), axial T2-weighted turbo spin-echo imaging (TR/TE 3000 ms/80 ms, 400×319 matrix), and axial FLAIR turbo spin-echo imaging (TR/TE/TI 10000 ms/125 ms/2800 ms, 532×249 matrix) with a field of view (FOV) of 230 mm and a slice thickness of 5 mm. After the injection of gadolinium-based

contrast agent (0.1 mmol/kg gadobutrol, Gadovist, Bayer Schering Pharma), 3D contrast-enhanced T1-weighted gradient-echo images were acquired with the following parameters: a TR/TE of 9.9 ms/4.6 ms, 224×224 matrix, an FOV of 220 mm, and a slice thickness of 1 mm.

APT-weighted Image Processing

To account for the B_0 field heterogeneity effect in APT imaging, the full Z-spectrum acquired using WASSR technique was fitted for all offset frequencies using a 12th-order polynomial on a voxel-by-voxel basis. The fitted curve was then interpolated at a higher spectral resolution (1 Hz), and the lowest signal in the fit was assumed to be an actual water resonance frequency. The measured displacement between the actual and ideal the water resonance frequency (0 Hz) resulted in the water centre frequency offset [27]. The acquired APT-weighted data at the saturation frequency offsets (± 3.0 , ± 3.5 , ± 4.0 ppm) were interpolated over the offset range and shifted using the estimated water centre frequency offset. Finally, magnetization transfer ratio asymmetry (MTR_{asym}) at ± 3.5 ppm was calculated using shift-corrected APT-weighted image data as follows [6]:

$$MTR_{asym}(+3.5\text{ppm}) = \frac{S_{sat}(-3.5\text{ppm}) - S_{sat}(+3.5\text{ppm})}{S_0},$$

where S_0 and $S_{sat}(\pm 3.5 \text{ ppm})$ are MR signals without and with saturation RF pulses, respectively, at the saturation offset frequency downfield (+3.5 ppm) and upfield (−3.5 ppm) from the water centre frequency (0 ppm). All data processing was performed offline using Matlab (MathWorks, Natick, MA).

Before ROI analysis, anatomical T1- and T2-weighted imaging, and contrast-enhanced T1-weighted imaging (in tumour cases) were coregistered to raw APT-weighted images using statistical parametric mapping SPM12 (Wellcome Trust Centre for Neuroimaging, University College London; <http://www.fil.ion.ucl.ac.uk/spm/>). First, the anatomical image data and the raw APT-weighted image data from all the patients enrolled in this study were converted to AnalyzeTM (www.mayo.edu/bir/PDF/ANALYZE75.pdf) data format. Then the converted anatomical images were coregistered to the raw APT-weighted images using a batch script mode supported by SPM12. The coregistered anatomical images were then compared side-by-side with the raw APT images using Medical Image Processing, Analysis, and Visualization (MIPAV: <http://mipav.cit.nih.gov>, Version 7.2.0) for brain anatomical landmarks and lesion contours by one radiologist with 5 years of experience in neuroradiology (Fig. 1a). ROIs were carefully defined in the coregistered anatomical images within the enhancing portion, haemorrhage, and normal-appearing white matter of each patient by the radiologist. When a haemorrhage was observed at different stages in a single image slice of a patient, e.g., acute and subacute stages, ROIs were drawn separately in the corresponding areas, and logical operations were performed on the binary masks from each ROI. As the exact onset time of a haemorrhage is often unclear clinically, the stage of haemorrhage was determined primarily based on T1- and T2-weighted images. An acute haemorrhage was defined for a region showing hypointense signal on both T1- and T2-weighted images. A haemorrhage shown with hyperintense signal on T1-weighted image

was considered to be subacute regardless of signal intensity on T2-weighted image [22]. Based on this MR signal characteristics, ROIs were drawn at different hemorrhagic stages as follows: ROIs were defined independently in both of the T1- and T2-weighted images. If a unique hemorrhagic stage was observed, a final ROI was determined as the intersection of the two ROIs. If different hemorrhagic stages were observed in both T1- and T2-weighted images at a common slice location, e.g., acute and subacute stages, then two different ROIs were drawn independently on the T1-weighted image, one with hyperintense signal and the other with isointense signal intensity, representing each stage, and a single ROI was drawn on the T2-weighted image enclosing a whole hemorrhagic lesion. All these ROIs were converted into binary masks, and logical operations on the masks were performed: First, “AND” operation was performed between the two ROI masks from the T1-weighted image and the single ROI mask from the T2-weighted image to include the common hemorrhagic lesions. Then the two ROI masks from the T1-weighted image were processed with mutually exclusive operation resulting in acute and subacute ROI masks, respectively, excluding overlapping regions between the two ROI masks (Fig. 1). Similarly, to define ROI of enhancing component in the tumour group, two ROIs were drawn including regions showing hyperintense signal on each of the T1-weighted and contrast-enhanced T1-weighted images. Next, the ROI mask of T1-weighted image was subtracted from that of contrast-enhanced T1-weighted image to include only enhancing component within the ROI, resulting in the mask of enhancing portion. Subsequently, each ROI mask was transferred to MTR_{asym} maps to obtain the values at lesions corresponding to each component. Computed tomography (CT) images were also used to evaluate haemorrhage stage in 13 patients who underwent CT within three days before the MRI scans. Haemorrhages were observed as high attenuation at acute stage and iso-attenuation at subacute stage in the patients, and correlated well with the MR staging.

Statistical Analysis

MTR_{asym} values were obtained from the four components (acute haemorrhage, subacute haemorrhage, enhancing portion and normal white matter) when presented in each patient. MTR_{asym} values were compared using a linear mixed model that included the fixed effects for each group and component, the interaction between each group and component, and random intercepts for each patient [29]. Covariance between all components was assumed to be equal. Statistical analyses were performed using the SAS software package, version 9.2 (SAS Institute Ind., Cary, NC, USA) and MedCalc, version 9.3.6.0 (MedCalc Software, Mariakerke, Belgium). *P* values of less than 0.05 were considered to be statistically significant.

Results

MTR_{asym} values were $3.68\% \pm 1.47\%$ in acute haemorrhage regions, $1.64\% \pm 0.83\%$ in subacute haemorrhage regions, $2.65\% \pm 0.92\%$ in the enhancing portion, and $0.38 \pm 0.65\%$ in normal appearing white matter. Among the 16 patients with tumours, five exhibited acute haemorrhages, two exhibited subacute haemorrhages, and nine exhibited both acute and subacute haemorrhages within the lesions. Among the seven patients with non-tumorous lesions, two exhibited acute haemorrhages, one exhibited subacute haemorrhages, and four

exhibited both acute and subacute haemorrhages within the lesions. In the tumour group, MTR_{asym} values were $3.69\% \pm 1.52\%$ in acute haemorrhage regions, $1.443\% \pm 0.84\%$ in subacute haemorrhage regions, $2.65\% \pm 0.92\%$ in the enhancing portion, and $0.24\% \pm 0.59\%$ in normal-appearing white matter (Table 1). In the non-tumour group, MTR_{asym} values were $3.67\% \pm 0.54\%$ in acute haemorrhage regions, $1.83\% \pm 0.82\%$ in subacute haemorrhage regions, and $0.71\% \pm 0.39\%$ in normal-appearing white matter. Figure 2 shows the representative high MTR_{asym} values in acute haemorrhage in both tumour and non-tumour patients. According to the linear mixed model, the P value for the interaction effect between each group and component was 0.896, indicating that the distribution of MTR_{asym} values among components was not significantly different between the tumour and non-tumour groups. MTR_{asym} in acute haemorrhage regions between the tumour and the non-tumour groups was not significantly different (3.69% vs. 3.67% , $P = 0.967$). In addition, MTR_{asym} in subacute haemorrhage regions between the tumour and the non-tumour groups was not significantly different (1.44% vs. 1.83% , $P = 0.774$). Acute haemorrhage regions showed significantly higher MTR_{asym} values than subacute haemorrhage regions in both the tumour (3.69% vs. 1.44% , $P < 0.001$) and non-tumour (3.67% vs. 1.83% , $P < 0.001$) groups. Figure 3 shows a representative case with hemorrhagic metastasis demonstrating higher MTR_{asym} in acute haemorrhage regions than in subacute haemorrhage regions. In the tumour group, MTR_{asym} was significantly higher in acute haemorrhage regions than in the enhancing portion (3.69% vs. 2.65% , $P < 0.001$), and it was also significantly higher in the enhancing portion than in normal-appearing white matter (2.65% vs. 0.24% , $P < 0.001$).

Discussion

We found that MTR_{asym} was relatively high in acute haemorrhage regions regardless of the underlying pathology, and it was even higher than the MTR_{asym} in the enhancing portion of tumours. A recent investigation on porcine blood reported increased MTR_{asym} in the whole blood, plasma and red blood cells, and it was consistent with our observation of high MTR_{asym} in the hemorrhagic portion [23]. The authors explained that high MTR_{asym} values may be attributed to the high levels of amino acids, proteins and peptides in the blood. Another animal study using a rat model also demonstrated an increased APT-weighted signal in hyperacute ICH, suggesting that the high APT effect may be attributable to abundant erythrocytes, plasma proteins, and peptides, as well as higher pH in the hematoma [24]. In tumours, enhancing portions yielded higher MTR_{asym} values than normal-appearing white matter, which is in accordance with the findings from previous studies demonstrating increased MTR_{asym} in malignant tumours due to increased mobile proteins and peptides caused by increased cellular proliferation [4, 5, 7, 11, 18, 19]. However, MTR_{asym} in acute haemorrhage regions was higher than that in the enhancing portion of tumours. These findings are significant because APT imaging is increasingly used not only in brain tumours but also in cerebral ischemia, and these conditions are commonly associated with haemorrhages. Specifically, benign tumours with haemorrhages may show increased APT-weighted signal intensity not due to increased cellularity but due instead to acute hemorrhages, which can be misinterpreted as a high grade tumour based on APT-weighted image without prior knowledge of the increased APT-weighted signal in acute haemorrhages.

It is interesting to note that subacute haemorrhages showed lower MTR_{asym} than acute haemorrhages. ICH can show various signal characteristics, given that hematomas undergo biological and biochemical changes as they evolve. In the subacute stage, deoxyhaemoglobin progresses to methemoglobin, which renders iron atoms more accessible to water protons. Consequently, T1 is markedly shortened due to proton-electron dipole-dipole interactions [21, 22]. There are many biological factors that contribute to APT signal intensity including protein and water contents, pH and temperature [14], and spin-lattice relaxation rate ($1/T1$) [6, 17, 30], all of which can contribute to MTR_{asym} in hematoma. A previous *in vivo* study reported that the conventional magnetization transfer (MT) effect by macromolecules was significantly lower in acute or subacute haemorrhage than in normal white and gray matter and lower in subacute haemorrhage than in acute haemorrhage [31]. As haemorrhage evolves macromolecules are diluted and degraded, and consequently conventional MT is expected to decrease in haemorrhage over time [31]. Considering these results on the conventional MT effect in acute and subacute stages, it is probable that, MTR_{asym} in hematoma was not dominated by changes in conventional MT but by the CEST effect. Because higher MTR_{asym} reflects both CEST and MT effects competing each other at opposite sites, i.e., downfield and upfield from water resonance, respectively, larger estimates of the MTR_{asym} in acute haemorrhages than in subacute haemorrhages demonstrate that the change in the CEST effect may dominate over the change in the MT effect between the two stages [9, 32, 33]. Although it has recently been shown that the T1 effect in APT would be compensated by water content using animal model and MTR_{asym} at 3.5 ppm is a reliable and valid metric for APT imaging of glioma at 3 T, further investigations would be necessary to separate upfield and downfield signal contributions for isolation of the APT-weighted signal in the presence of the other effect, e.g., NOE [34–36].

In this study, MTR_{asym} in normal brain tissue was almost zero, a value consistent with previous reports that used the same saturation RF power and irradiation setup [7, 37]. Also, in this study, APT imaging was performed using 3D GRASE [25] with six saturation frequency offsets as described previously [26]. The effect of magnetic field heterogeneity was corrected using WASSR technique to improve the accuracy of the APT effect, which is largely dependent on field heterogeneity-induced frequency shift [25–27]. The correction scan was acquired by encompassing a frequency range where typical field heterogeneity occurs in the brain and by using relatively weak RF power and short durations for minimum CEST and MT effect within the offset range. Therefore, we were able to obtain 3D APT-weighted images with improved SNR and full lesion coverage in a clinically suitable time frame.

There were several limitations to our study. First, no exact biochemical features of haemorrhages were correlated with MTR_{asym} . However, our results were consistent with previous phantom and animal studies demonstrating increased MTR_{asym} in haemorrhages [23, 24]. Further investigations with phantom and surgical specimens would provide more accurate results by isolating upfield and downfield signal contributions in APT-weighted effects. Second, the number of patients in each group was relatively small. The high MTR_{asym} in acute hemorrhagic lesions, however, was consistently observed in both tumour and non-tumour groups and significant differences in MTR_{asym} were found between acute and subacute haemorrhages using a linear mixed model. Future studies should include larger

numbers of patients in each group, in addition to more diverse tumour cases. Third, although careful investigation explored the stages of haemorrhages and tissue types based on conventional MRI and CT, there might have been mixed stages of haemorrhages (Fig. 3) or intermingled tissue types between haemorrhages and tumour cells in the tumour group. Considering that the aim of this study was to characterize APT-weighted signals in acute and subacute hemorrhagic stages regardless of tumour presence, we expect that our study may help in interpreting hemorrhagic brain lesions in pathologic environments analogous to the environments investigated in this study.

In conclusion, acute haemorrhage showed high MTR_{asym} regardless of underlying pathology, whereas subacute haemorrhage showed lower MTR_{asym} than acute haemorrhage. These results can aid in the interpretation of APT imaging in hemorrhagic brain lesions.

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Abbreviations and acronyms

APT	Amide proton transfer
CEST	Chemical exchange saturation transfer
MT	Magnetization transfer
MTR_{asym}	Magnetization transfer ratio asymmetry
ICH	Intracranial haemorrhage
RF	Radiofrequency
TR	Repetition time
TE	Echo time
TI	Inversion time
SNR	Signal-to-noise ratio
FLAIR	Fluid attenuated inversion recovery
PPM	Parts per million

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Key points

- Acute haemorrhages show significantly higher MTR_{asym} values than subacute haemorrhages.
- MTR_{asym} is higher in acute haemorrhage than in enhancing tumour tissue.
- MTR_{asym} in haemorrhage does not differ between tumorous and non-tumorous lesions.

Figure 1.

Definition of region of interest (ROI). After coregistration between conventional images and raw APT imaging, ROIs were drawn on T1-weighted imaging for acute and subacute lesions, respectively. Another ROI was drawn on T2-weighted imaging representing a whole hemorrhagic lesion. Then, logical operations on the masks were performed for excluding overlapping lesions between acute and subacute hemorrhagic lesions. Subsequently, these ROI masks were transferred to the coregistered MTR_{asymp} maps.

Figure 2.

MRI of metastasis (a,b,c) and cavernous malformation (d,e,f). A T2-weighted image (a) shows a cystic lesion with a fluid-fluid level due to an internal haemorrhage, and a contrast-enhanced T1-weighted image (b) shows irregular peripheral enhancement. The corresponding MTR_{asym} map (c) demonstrates a high signal within the haemorrhage as well as in the enhancing portion. T2- (d) and T1-weighted (e) images demonstrate a multiloculated cystic lesion with an acute haemorrhage, suggestive of cavernous malformation. MTR_{asym} is also elevated (f).

Figure 3.

MRI of hemorrhagic metastasis. At the periphery, the lesion shows isointensity on the T1-weighted image and hypointensity on the T2-weighted image, both suggestive of acute haemorrhage. On the other hand, the central portion of the lesion shows hyperintensity on both T1- (a) and T2-weighted images (b), suggestive of a late subacute haemorrhage. The MTR_{asym} map (c) demonstrates a higher signal in the acute haemorrhage region than in the subacute haemorrhage region.

Table 1

MTR_{asym} (%) in each portion of the hemorrhagic lesions in non-tumor and tumor groups (mean $\pm$ standard deviation).

	Acute hemorrhage	Subacute hemorrhage	Enhancing portion	Normal appearing white matter
Tumor (n=16)	3.69 $\pm$ 1.52	1.44 $\pm$ 0.84 *	2.65 $\pm$ 0.92 *	0.24 $\pm$ 0.59 *
Number of lesions	14/16	11/16	16/16	16/16
Non-tumor (n=7)	3.67 $\pm$ 0.54	1.83 $\pm$ 0.82 *	NA	0.71 $\pm$ 0.39 *
Number of lesions	6/7	5/7		7/7
P values **	0.967	0.774	NA	0.317

* MTR_{asym} values that are significantly different from those of acute hemorrhage in each group (P value < 0.05).

** P values from comparisons between tumor and non-tumor in each component.