INTRODUCTION

Molecular imaging using endogenous molecules has generated a lot of interest because the methodology does not have the adverse effects of gadolinium (Gd) contrast agents and has clinical benefits in pediatric patients or patients with a contraindication for the use of an exogenous contrast agent. Chemical exchange saturation transfer (CEST) imaging has been introduced as a potentially useful technique that provides contrast by amplifying the signal from endogenous molecules. The CEST technique uses selective radiofrequency (RF) saturation of the “protons of interest” and obtains contrast from the signal change in the bulk water, where saturated protons are subsequently transferred and they cause decreased signals in the water. The use of the signal from large bulk water greatly amplifies the sensitivity and enables to detect a relatively small amount of molecules at a high spatial resolution. Among the different types of CEST imaging, amide proton transfer (APT) imaging is the most widely used technique. It provides information on cellular proteins and physicochemical properties of tissue by using abundant amide protons that resonate at 3.5 ppm downfield from the water resonance. In our present review, we focus on the basic mechanism underlying APT imaging, the current clinical uses of APT in brain glioma, and its potential future use in cases of stroke. We also critically
review several pitfalls in APT imaging and some promising CEST approaches for stroke imaging.

THEORETICAL BACKGROUND OF APT IMAGING AND ISSUES REGARDING THE ORIGIN OF SIGNAL SOURCE

Theoretical Background of APT Imaging

APT imaging is a type of CEST imaging, in which off-resonance RF irradiation leads to magnetization of the “protons of interest,” and the signal is detected indirectly through the chemical exchange with bulk water protons. Amide protons (protons-of-interest) resonate 3.5 ppm downfield from the water resonance (which is 8.25 ppm, compared to 4.75 ppm for water) via a chemical shift in the nuclear magnetic resonance (NMR) spectrum. In hydrogen 1 \(^1\)H MR spectroscopy, the signal peak comes directly from the solute proton in the water pool. Since the abundance of metabolites is much less than that of water protons in tissue (in the concentration range of \(\mu\)M to mM) (1), the signal-to-noise ratio is low and a long scanning time is required for resolution. On the other hand, CEST indirectly reflects the solute proton via the signal of the abundant water pool. When a selective RF pulse is applied at 3.5 ppm, the proton attached to the amide bond becomes saturated. Subsequently, these saturated protons move to the neighboring water and exchange with the free water protons. A single transfer of saturation would be insufficient to cause any discernible effect on water pool (2), but prolonged irradiation causes a large amount of water protons to become saturated by the chemical exchange. Fig. 1 shows the CEST mechanism. The solute protons are saturated at their specific resonance frequency shown in \(^1\)H NMR with a selective RF pulse. The saturation effect is transferred to water (\(H_2O, 4.75\) ppm) at an exchange rate, and this effect becomes visible on the water signal. Due to this CEST effect on abundant water protons, labile protons of low-concentration solutes can be imaged indirectly. Considering the effect of signal amplification of CEST compared to MR spectroscopy, there is nearly a ~700-fold sensitivity improvement in CEST of glutamate molecules (3) compared to conventional \(^1\)H MR spectroscopy at physiological concentrations and temperatures. Fig. 2 shows the difference spectra at 3 ppm points on the where the ratio of the CEST difference spectrum to NMR glutamate resonance at 2.3 ppm is ~700.

For quantitative representation of relative signal enhancement by the CEST effect, magnetization transfer ratio asymmetry \(\text{MTR}_\text{asym}\) is determined as follows:

\[
\text{MTR}_{\text{asym}} (+\Delta\omega) = \text{MTR} (-\Delta\omega) - \text{MTR} (+\Delta\omega)
\]

where both \(+\Delta\omega\) and \(-\Delta\omega\) are the chemical shift frequencies of the amide protons and its opposite with respect to water, respectively. The equation for APT imaging is as follows:

\[
\text{MTR}_{\text{asym}} (+3.5\ \text{ppm}) = [S_{\text{sat}} (-3.5\ \text{ppm}) - S_{\text{sat}} (+3.5\ \text{ppm})] / S_0
\]

This analysis is applied to remove the direct water saturation (i.e., the spillover effect) (4-6) and broad macromolecular magnetization transfer contrast (MTC) from the off-resonance RF irradiation (7).

Issues Regarding the Origin of Signal Source in APT Imaging

The water longitudinal relaxation time \(T_{\text{1w}}\) and water proton concentration can affect the APT signal (2, 7, 8). With respect to
brain glioma, Scheidegger et al. (7) showed that the contrast between glioma and normal brain tissue is dominated by broad macromolecular MTC rather than chemical exchanges from mobile protons. On the other hand, a recent research by Zhou et al. showed the APT signal in glioma is dominated by the mobile amide proton content as well as the amide proton exchange rate (9). The study also showed that the effect of increasing $T_{1w}$ on the APT signal was mostly eliminated by the effect of increasing water content in a tumor. Whereas Xu et al. (10) showed that the APT signal in tumors was not significantly different from that in normal brain tissues after correction of spillover, magnetization transfer (MT) and $T_1$ effects. Along with the above mentioned signal sources, recent studies showed contamination of the APT signal from amine exchange (8) and aromatic nuclear Overhauser enhancement (NOE) (11). The issues regarding the signal source in APT imaging are yet to be clarified, but understanding the possible contributors to APT imaging is important in clinical practice as a potential molecular imaging biomarker.

**PRACTICAL CONSIDERATIONS FOR APT IMAGING IN ACQUISITION AND PROCESSING**

**$B_0$ and $B_1$ Inhomogeneity**

Static magnetic field ($B_0$) inhomogeneity introduces a shift in all resonances in the Z-spectrum, which results in an artificial APT effect in MTR asymmetry analysis (12, 13). Here, the Z-spectrum reflects the RF saturation effects on water as a function of saturation frequency offset relative to water (14). Since $B_0$ inhomogeneity scales with field strength, it is particularly significant at higher magnetic fields than at lower magnetic fields. The irradiated RF field ($B_1$) inhomogeneity can result in increased direct water saturation and insufficient saturation of the exchanging pool, which can then lead to inaccuracies in APT analysis. However, in the clinical MRI field strength, $B_0$ inhomogeneity often results in more significant errors in APT analysis than $B_1$ inhomogeneity does, if spatially uniform saturation is achieved (15).

Correction of $B_0$ inhomogeneity can be accomplished by field mapping using the gradient-echo sequence (16) or by identifying the water resonance frequency and shifting either the partial or whole range of Z-spectrum to align with the center frequency, which has been developed in the form of water saturation referencing (13). Other correction methods include acquisition using the entire (12, 17-19) or partial (20) $Z$-spectrum or using multiple echoes (21), for estimation of $B_0$ inhomogeneity simultaneously with acquisition of Z-spectrum.

**Specific Absorption Rate**

In clinics, APT imaging sequence is required for MR image acquisitions with RF irradiation at multiple saturation frequencies using relatively weak and prolonged saturation RF pulses. Therefore, the first and foremost challenge for practical applications of APT in clinical MRI devices is to stay within the FDA-allowed specific absorption rate (SAR) with RF irradiation long enough to obtain the maximum saturation under a given RF duty cycle limit supporting the maximum lesion coverage and a clinically feasible scan time. The SAR can be reduced by using weaker or shorter RF pulses at the cost of a smaller APT effect and/or by using parallel imaging in which the repetition time (TR) can be relatively increased by reducing the phase-encoding steps. This can result in a reduction of the average SAR, if the same saturation RF schemes are used with the same scan time. On the other hand, if TR is increased with a constant SAR limit, the APT effect can be increased by using a stronger saturation RF power in some $B_1$ limited applications.

**APT Imaging Pulse Sequence**

Even though an APT sequence satisfies the minimum SAR requirement, it is not trivial to achieve a long duration of RF irradiation, as clinical scanners cannot generate RF irradiation with a high duty cycle, limiting the typical saturation RF length to 250–500 ms. Therefore, pulsed saturation approaches are commonly used in clinical MRI scanners, wherein a train of saturation RF pulses is used with crusher gradients. Alternatively, one or multiple short saturation RF pulses are inserted into the two-dimensional or three-dimensional (3D) gradient-echo (22, 23), segmented echo-planar imaging (24, 25), turbo spin-echo (19, 26, 27) or gradient- and spin-echo image readout (12, 18). This leads to accumulation of the saturation effect for slowly exchanging species, e.g., amide protons, due to a relatively short imaging TR, which is much less than the relaxation time ($T_1$) of tissue.

**APT Imaging Data Processing**

There are many confounding CEST effects that contribute to
the Z-spectrum, and as a consequence, APT analysis. For APT imaging, MTR\textsubscript{sym} (+3.5 ppm) can be broken up into two components (7, 28):

$$\text{MTR\textsubscript{sym}} (+3.5 \text{ ppm}) = \text{MTR\textsubscript{sym}} (+3.5 \text{ ppm}) + \text{APTratio} (+3.5 \text{ ppm})$$

The MTR\textsubscript{sym} value represents other signal sources, including the asymmetric macromolecular MTC effect and the upfield NOE effect of mobile polypeptides, lipids, and metabolites in tissue (9, 25, 29, 30). In order to address these effects, several methods have been developed and utilized for isolating the respective CEST components that contribute to the Z-spectrum. These methods include the use of Lorentzian line shapes (30) with linear (31) or probabilistic (32) combinations to obtain the amplitude, width and position of each component peak, or application of modified Bloch-McConnell equations (33) using the number of CEST components based on a physiological model (32) or contrast agent design (33). Also, the three-offset method with use of empirically determined lower/upper boundary offsets (10, 34) or Laplacian Lorentzian model (35) has been introduced. While model fitting of the data is performed essentially via non-linear least-squares, a form of preprocessing (e.g., smoothing) of acquired CEST data has been performed using a cubic spline (36-38) before further analyses. Recently, ratiometric approaches have been utilized for pH mapping in CEST MRI (38-42) and APT imaging (43). This approach utilizes the CEST effects between different exchangeable groups (37, 38, 41), saturation RF amplitudes (39, 42), or flip angles (43), resulting in an concentration-independent signal which maps the pH values from pH calibration signal and APT contrast ratio, respectively.

**CLINICAL APPLICATIONS**

**Brain Tumor Imaging**

In the interest of reflecting mobile protein contents and peptides, APT imaging has been applied to brain tumor imaging in both experimental and clinical studies. It has been used in diverse applications to evaluate brain tumors: characterizing a tumor and its differential diagnosis, tumor grading as an index for tumor proliferation, and treatment monitoring.

**Tumor Extent**

The first human experimental result for APT in a brain tumor was investigated to quantify the APT effect in a clinical MRI system (27). Conventional MR imaging is often unsatisfactory for delineating tumor boundaries. This imaging includes T2-weighted imaging (T2WI) in which high signal intensities arise from either tumor infiltration or peritumoral edema and Gd-enhanced, T1-weighted imaging (T1WI), in which the contrast-enhancing portions represent the regions with disruption of the blood-brain barrier. Fig. 3 shows the APT image and different types of MR images at 3T for a patient with a meningioma. The mean and standard error of the APT are -0.1 ± 0.04 for the tumor and -2.0 ± 0.08 for the edema. Note that APT differentiates an edema region from the tumor. The increased APT contrast is predominantly due to increased protein/peptide contents (18, 27, 44), and the extent of this increased contrast is smaller than that in T2WI but larger than that in enhanced T1WI. The source of the increased APT asymmetry was also explained by a higher intracellular pH range (up to approximately 0.1 pH units) for many brain tumor types (45) compared to that of the normal brain tissue. An elevated intracellular pH increases the exchange rate, thus increasing the APT contrast.

**Proliferative Index and Tumor Grading**

Since high-grade tumors show accelerated cell proliferation and increased protein expression compared to low-grade tumors (46), APT imaging that indirectly reflects protein content may be suitable for tumor grading. Other advanced MR imaging techniques used in patients with brain gliomas (i.e., contrast enhancement, diffusion-weighted, and perfusion-weighted imaging) have been insufficient for tumor grading. A recent study showed that APT imaging had a linear positive correlation with the pathologic tissue proliferative index (Ki-67) ($r = 0.43, p = 0.01$) and cell density ($r = 0.38, p < 0.05$) (47).

Among the existing relevant in vivo molecular MR imaging techniques, choline-containing compounds on MR spectroscopy are known to reflect protein expression and proteolysis (48) and can be compared with APT imaging in terms of the tumor proliferative index. In a lesion-by-lesion correlation analysis of the solid tumor portion, the choline-to-creatine (Cho/Cr) ratio was found to moderately correlate with APT asymmetry ($r = 0.49, p < 0.001$) (Fig. 4) (47). In Fig. 4B, the Cho/Cr ratio in the same 1.5 cm$^3$ MR spectroscopy was 5.43. In this study, the diagnostic performance for tumor grading was found to be comparable to the Cho/Cr ratio. Although the correlations between APT imaging
and MR spectroscopy were not conclusively strong, the result implies that APT imaging can be a potential alternative methodology for MR spectroscopy considering the tumor proliferative index. It is worth noting that APT imaging has advantages in terms of its coverage of the entire lesion, its relatively high resolution and its short imaging time (< 10 min) with a recent 3D acquisition technique; therefore, this method enables quantitative measurement of the entire lesion. Coverage of the entire lesion with APT imaging enables us to identify the most active parts of the tumors and may guide stereotactic biopsy and local therapies in the future.

Differential Diagnosis from Mimics

The differential diagnosis between necrotic, contrast-enhancing, low-grade tumors and high-grade tumors is often difficult with use of contrast-enhanced or advanced imaging with perfusion or diffusion-weighted imaging. Because a high-grade tumor has higher APT asymmetry due to its accelerated cell proliferation-derived high protein content, APT imaging can be used to differentiate a low-grade tumor mimicking a high-grade tumor. In a previous study including 19 low-grade tumors (i.e., three astrocytomas, seven oligodendrogliomas, three pleomorphic xanthoastrocytomas, four pilocytic astrocytomas, and two hemangioblastomas), APT asymmetry was found to be significantly higher in high-grade tumors than in low-grade tumors, as shown by the examples presented in Figs. 5, 6 (49). In terms of diagnostic performance, adding APT imaging to dynamic susceptibility contrast MR perfusion imaging significantly improved the diagnostic performance. This implies that APT imaging may be more effective than MR perfusion imaging in determining the grade of a contrast-enhanced tumor.

Atypical primary central nervous system lymphoma (PCNSL)
can mimic glioblastoma, and a differential diagnosis between the two entities is important, as the mainstay of treatment for glioblastoma is maximal safe resection while PCNSL requires biopsy followed by chemotherapy. Eleven PCNSL patients were compared to 21 high grade glioma patients using APT imaging on 3T (50). The PCNSLs showed lower maximum and more homogeneous APT signals and higher MTR asymmetry than high-grade glioma lesions. The author explains that the signal difference was

![Image of APT imaging results]

**Fig. 4.** Correlation of APT asymmetry with Cho/Cr ratio on MR spectroscopy.  
**A.** Images and graphs of a 42-year-old patient with anaplastic oligodendroglioma (World Health Organization grade 3) show the process of transferring the same 1.5 cm³ from MR images to APT images, followed by histogram analysis of the APT solid (range: 28% to approximately 8%).  
**B.** The scatter plot, in which data points were fitted to the line, shows the relationship between Cho/Cr at MR spectroscopy and APT-solid measurement in the same voxel of interest in all solid lesions in all patients. Reprinted from Park et al. (47) with permission.  
APT = amide proton transfer, Cho/Cr = choline-to-creatine, MR = magnetic resonance, NAA = N-acetylaspartate
related to the histological characteristics of PCNSL, which has a higher N/C ratio (i.e., less cytoplasm and more nuclei and membranes) compared to high-grade glioma.

Therapeutic Monitoring

Identifying an imaging biomarker that reflects the therapeutic response is clinically important to determine whether to discontinue the current treatment and/or to initiate other treatment options. The first experimental study of APT for therapeutic monitoring of glioblastoma was performed for quantitative assessment of the treatment response during chemotherapy (51). One course of temozolomide (TMZ 80 mg/kg i.p. for three days) was applied to a mouse tumor model, and APT asymmetry was measured before and after treatment at a one-week interval. APT asymme-

Fig. 5. These images were obtained in a 64-year-old man with a World Health Organization grade 1 tumor (hemangioblastoma).

A. The contrast-enhanced T1-weighted MR image demonstrates a contrast-enhancing solid mass with a cyst in the right cerebellar hemisphere.
B. The dynamic susceptibility contrast MR image shows that the normalized cerebral blood volume is remarkably high in the corresponding contrast-enhancing solid mass.
C. The APT image demonstrates the APT signal intensity.
D. The histogram distribution of the signal intensity is relatively low in the solid portion, but it is remarkably high in the cystic portion, suggesting a low-grade tumor.

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APT = amide proton transfer, MR = magnetic resonance
try was decreased in the treated groups, but it was increased in the control group. Interestingly, although there were no detectable differences in tumor volume, cell density, and apoptosis rate between the two groups, the cellular proliferative index (Ki-67) levels were substantially reduced in the treated tumors (51). The correlation between Ki-67 and APT asymmetry indicates that APT imaging may serve as a sensitive biomarker of early treatment response. This is particularly important in neuro-oncologic imaging, where a treatment-related reaction known as “pseudoprogression” often results in an increase in the contrast-enhancing lesion.

Two clinical studies, one focusing on pseudoprogression and

**Fig. 6.** Images obtained in a 75-year-old man with World Health Organization grade 4 tumor (glioblastoma).

A. The contrast-enhanced T1-weighted MR image demonstrates a necrotic contrast-enhancing mass in the right parietal lobe.

B. The DSC image shows that the nCBV is remarkably high in the corresponding contrast-enhancing solid mass.

C. The APT image demonstrates the increased APT signal intensity.

D. The histogram distribution is high in the solid portion and it is relatively low in the necrotic portion, suggesting a high-grade tumor.

Reprinted from Park et al. (47) with permission.

APT = amide proton transfer, DSC = dynamic susceptibility contrast, nCBV = normalized cerebral blood volume.
the other focusing on true progression, are available for evaluating the treatment response of newly diagnosed glioblastoma.

One study showed that the diagnostic performance of APT imaging was 0.98, applying the area-under-the-curve using a receiver operating characteristic analysis with a sensitivity of 85.0% and a specificity of 100% (52). Another study showed the added value of APT imaging to conventional and perfusion MRI for post-treatment glioblastomas (53). Adding APT imaging to conventional and perfusion MRI significantly improved the diagnostic performance: from 0.58–0.74 to 0.89–0.91. Moreover, the combination of contrast-enhanced T1 weighted imaging, perfusion-weighted imaging (nCBV\textsubscript{90}), and APT imaging (90th percentile of the signal, APT\textsubscript{90}) resulted in greater diagnostic accuracy for differentiating treatment change from progression than did the combination of contrast-enhanced T1 and perfusion-weighted imaging only. These studies showed promising results which suggest that combining APT imaging with multiparametric MRI assessment will be beneficial for treating glioblastoma patients.

Fig. 7. These images were obtained by CEST MR imaging of G47D-empty viruses and G47D-LRP-infected cell lysates. **A.** The representative MTR\textsubscript{asym} map shows phantoms that contained lysates of D74/HveC cells infected with either G47D-empty viruses (upper) or G47D-LRP (lower). **B.** This graph of the MTR\textsubscript{asym} induced by G47D-LRP in these cells shows that a significantly higher MTR\textsubscript{asym} (*\textit{p} = 0.01) was observed in D74/HveC cell lysates infected with G47D-LRP (1.52\% ± 0.06) compared to those infected with G47D-empty viruses (1.0\% ± 0.02).

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CEST = chemical exchange saturation transfer, LRP = lysine-rich protein, MR = magnetic resonance, MTR = magnetization transfer ratio

Fig. 8. This graph shows the measurement of ischemic brain metabolites with point-resolved spectroscopy. Reprinted from Sun et al. (57) with permission.

\text{Cho/Cr = choline-to-creatine, NAA = N-acetylaspartate, DWI = diffusion-weighted imaging, Glx = glutamate/glutamine, Lac = lactate, ROI = region-of-interest}

\begin{align*}
\text{Normalized MTR_{asym}}
\end{align*}

\begin{align*}
\text{ empty} & \quad \text{LRP} \\
0\% & \quad 0\% \\
2\% & \quad 1.52\% ± 0.06 \\
4\% & \quad 1.0\% ± 0.02 \\
6\% & \quad 1.0\% ± 0.02 \\
\end{align*}

\text{Empty} \quad \text{LRP
Oncolytic virotherapy for brain tumors is currently undergoing phase I clinical trials. Oncolytic viruses have the potential to improve the treatment of incurable cancers (54) such as glioblastoma. It is difficult to image the delivery of replicating oncolytic viruses, but a recent experimental study showed the potential use of APT imaging on a 9.4-T magnet as a tool to visualize replicating oncolytic viruses (54). The MTR asymmetry was calculated for a frequency offset of 3.6 ppm for lysine-rich protein (LRP, which contains an exchangeable amide proton). Before and after oncolytic virotherapy (within 8–10 hours after injection), a significant increase in tumor APT asymmetry was observed for LRP containing virus-infected tumors but not for LRP empty virus-infected tumors \( (p = 0.02) \) (Fig. 7). The ability to noninvasively image oncolytic viruses in the acute stage of infection could be useful in the development of a future targeted therapy (54, 55).

### Future Use for Oncolytic Virotherapy

Oncolytic virotherapy for brain tumors is currently undergoing phase I clinical trials. Oncolytic viruses have the potential to improve the treatment of incurable cancers (54) such as glioblastoma. It is difficult to image the delivery of replicating oncolytic viruses, but a recent experimental study showed the potential use of APT imaging on a 9.4-T magnet as a tool to visualize replicating oncolytic viruses (54). The MTR asymmetry was calculated for a frequency offset of 3.6 ppm for lysine-rich protein (LRP, which contains an exchangeable amide proton). Before and after oncolytic virotherapy (within 8–10 hours after injection), a significant increase in tumor APT asymmetry was observed for LRP containing virus-infected tumors but not for LRP empty virus-infected tumors \( (p = 0.02) \) (Fig. 7). The ability to noninvasively image oncolytic viruses in the acute stage of infection could be useful in the development of a future targeted therapy (54, 55).

### Potential Utility of APT in Stroke Imaging—A Critical View

#### APT Imaging as a pH–Weighted Imaging Technique

How can APT imaging reflect the physico-chemical properties of tissue? This can be explained by using a two-pool exchange model (17) (i.e., a small solute pool and a large water pool, with no back exchange of saturated protons). The proton transfer ratio (PTR) for the amide protons (APTR) is derived as follows (17, 28):

\[
\text{APTR} = \frac{k \text{ [amide proton]}}{2 [H_2O] R_2^{\text{sat}} (1 - e^{-R_1^{\text{sat}}})}
\]

**Fig. 9.** These images were obtained at one day after the onset in a patient with a right middle cerebral artery territory infarction, and the APT image (right) demonstrates that APT signal intensity is relatively low in the regions of diffusion restriction (6.945%) compared to the contralateral normal white matter (0.457%).

**Fig. 10.** This is the CEST spectra of 10% (by weight) bovine serum albumin dissolved in phosphate-buffered saline with varying pH at 37°C. Reprinted from McVicar et al. (38) with permission. CEST = chemical exchange saturation transfer.
Potential Utility of APT Imaging in Stroke Patients

An animal model study using a 4.7-T scanner of hypoperfused brain tissue showed decreased APT asymmetry, where the lactate peak on MR spectroscopy was significantly elevated (57), as shown in Fig. 8. Spectra for Fig. 8 were acquired (TR/TE = 1000/144 ms, number of acquisitions = 1024) from two ROIs: 1) in the ipsilateral ischemic lesion, which appeared to be hyperintensive in diffusion-weighted images (b = 1000 s/mm²); and 2) in the contralateral normal area, to serve as the reference ROI. The displayed spectra were normalized by the choline signal, so that the change in brain metabolites can be easily achieved. Note that the lactate peak increases in the ischemic ROI.

A study on translating pH-weighted imaging to image human subjects to determine a surrogate metabolic imaging marker using APT was published (58). The study was performed by the application of pH-weighted imaging in healthy volunteers to show the potential utility of APT imaging using a 3-T scanner in stroke patients. The first and only clinical study of APT imaging in actual stroke patients was published in 2013 (22). In 10 patients with acute anterior or posterior infarction, APT imaging on a 3T MRI scanner was performed, and the APT asymmetry in the infarct core, final infarct volume, and at-risk tissue (lengthening time-to-peak on perfusion MRI) were compared with normal-appearing white matter (NAWM) in each patient. Ischemic regions in patients showed reduced APT asymmetry compared with NAWM (p = 0.003) (22). However, the findings were heterogeneous and larger clinical studies are needed to evaluate the potential future use of APT imaging in stroke patients.

A Critical View of APT Imaging in Stroke Patients

Fig. 9 shows a representative case of APT asymmetry in a patient with a large middle cerebral artery territorial infarction (1 day from the onset). APT acquisition was performed with a 3D spin-echo sequence on a 3T clinical MRI with an off-resonance RF pulse at 2 µT and saturation duration of 2 s. For the CEST spectrum, nine points of acquisitions were used [off-resonance Δω = -1540 ppm, ± 3.0 ppm, ± 3.5 ppm (3 points on + 3.5 ppm), and ± 4.0 ppm]. On visual analysis, APT imaging provided a mild negative contrast compared to the contralateral NAWM. However, a large portion of the posterior temporal lobe also showed a symmetric, negative contrast, which hampered the interpretation in terms of tissue acidosis.

Both technical and practical considerations for the use of APT imaging in stroke patients need to be addressed. First, the effect of B₀ field inhomogeneity and direct water saturation can obscure lesions in the vicinity of the cerebrospinal fluid space, including the cerebral convexity adjacent to the sulci, where an acute infarction typically occurs. Second, acute stroke patients need a fast imaging tool that is robust, which is limited by motion and noise in the currently available techniques. Third, CEST sensitivity is low according to pH changes in amide protons. Although the CEST effect is shown to be sensitive to changes in pH, the sensitivity of an amide proton was found to be lower than that of an amine proton, a faster-exchanging molecule in the physiologic range (i.e., pH 6.0–8.5) (3, 8, 38, 59). Finally, the interpretation of APT imaging in the subacute phase is not straightforward, and several factors can significantly increase APT asymmetry (i.e., proteolysis and inflammation are likely to increase the amount of mobile proteins) (22). This increase opposes the reduction in APT asymmetry caused by a reduced pH, thus limiting the interval window for APT imaging and interpretation in the subacute stage.

Future Considerations for Stroke Imaging

We may use the target labile protons of amine rather than amide in stroke imaging. For the amine proton, which has a peak centered around 3 ppm, the CEST effects appear to increase as pH decreases in the physiologic range (3, 8, 38, 60).

At pH 7, amine CEST asymmetry is reduced due to the well-known phenomenon of intermediate- to fast-exchange-mediated chemical shift averaging. The decrease in pH leads to a reduced
exchange rate, which reduces the chemical shift averaging effect and makes the amine proton visible. This opposite direction of the change in CEST asymmetry in the amine proton is important for stroke imaging, in which a positive contrast may be seen in regions of tissue acidosis. Furthermore, the greater sensitivity of an amine proton to pH changes, compared to that of an amide proton (Fig. 10), may render stroke imaging more feasible with the amine proton. Further clinical studies are warranted to achieve improvement of the acquisition technique and processing methods.

CONCLUSION

APT imaging has added a new dimension to in vivo molecular imaging by its ability to reflect mobile proteins and physicochemical properties of tissue. High sensitivity in reflecting protein contents enables various applications in brain tumor imaging in terms of diagnosis and treatment monitoring. However, the relatively low sensitivity of an amide proton in reflecting pH changes is a hurdle for the clinical application of APT to stroke imaging. For its future use in this regard, the acquisition technique and processing methods need further improvements and other pH-sensitive protons (i.e., amine protons) need to be investigated.

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임상에서 사용 가능한 아미드 수소 이동 영상: 기본 원리와 뇌종양 및 뇌경색에서의 현재 그리고 미래의 이용

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아미드 수소 이동 영상은 분자 영상의 새로운 기법으로 기존 분자 영상법보다 높은 민감도와 공간 해상도를 갖고 있다. 아미드 수소 이동 영상은 화학 교환 포화 이동(chemical exchange saturation transfer)의 한 종류로서 물 분자의 수소와 교환하는 특정 분자의 수소를 선택적으로 포화하여 영상의 대조도를 나타낸다. 본 종설에서는 문헌 고찰을 바탕으로 아미드 수소 이동 영상의 기본 원리에 대해 설명하고자 한다. 임상적인 이용은 두 가지 측면에서 다루어지며 첫째로는 조직 내 단백질 및 케터挎를 반영하여 뇌교종에서 진단 및 치료 반응의 평가에 대해, 둘째로는 조직 내 산성도를 반영하여 뇌경색에서 이용 가능성에 대한 것이다. 본 종설은 임상적 측면에 초점을 맞추어 향후 본 영상 기법의 임상 응용에 도움이 되고자 한다.

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