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Fast multi-slice pH-weighted chemical exchange saturation transfer (CEST) MRI with uneven segmented RF irradiation: pH-weighted amide proton transfer (APT) MRI of acute stroke

Phillip Zhe Sun^{1,*}, Jerry S. Cheung¹, Enfeng Wang^{1,2}, Thomas Benner¹, and A Gregory Sorensen¹

¹Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129

²Department of Radiology, 3rd Affiliated Hospital, Zhengzhou University, P.R.China

Abstract

Chemical exchange saturation transfer (CEST) MRI is a versatile imaging technique for measuring microenvironment properties via dilute CEST labile groups. Conventionally, CEST MRI is implemented with a long RF irradiation module, followed by fast image acquisition to obtain the steady state CEST contrast. Nevertheless, the sensitivity, scan time and spatial coverage of the conventional CEST MRI method may not be optimal. Our study proposed a segmented RF labeling scheme that includes a long primary RF irradiation module to generate the steady state CEST contrast and repetitive short secondary RF irradiation module immediately after the image acquisition so as to maintain the steady state CEST contrast for multi-slice acquisition and signal averaging. The proposed modified CEST MRI method was validated experimentally with a tissue-like pH phantom, and optimized for the maximal contrast-to-noise ratio (CNR). In addition, the proposed sequence was evaluated for imaging ischemic acidosis via pH-weighted endogenous amide proton transfer (APT) MRI, which showed similar contrast as conventional APT MRI. In sum, a fast multi-slice relaxation self-compensated CEST MRI sequence was developed, with significantly improved sensitivity.

Keywords

acute ischemia; amide proton transfer (APT); chemical exchange saturation transfer (CEST); pH; stroke

1. INTRODUCTION

Chemical exchange saturation transfer (CEST) MRI is a versatile imaging technique that can probe the interaction between dilute labile protons and bulk/tissue water to enable assessment of the local concentration of CEST agents and microenvironment properties such as pH and temperature (1-5). Because metabolites and polypeptides often contain exchangeable protons, CEST MRI has great promise for molecular imaging and in vivo applications (6-11). Particularly, a specific form of CEST MRI known as amide proton transfer (APT) MRI has been shown sensitive to pH, and thus may serve as a surrogate metabolic marker for imaging ischemic acidosis (12-15). As such, CEST MRI can provide

*Corresponding author: Athinoula A. Martinos Center for Biomedical Imaging Department of Radiology, MGH and Harvard Medical School Rm 2301, 149 13th street, Charlestown, MA 02129 pzhesun@nmr.mgh.harvard.edu Phone: 617-726-4060 Fax: 617-726-7422 .

information that complements data obtainable by conventional MRI methods, to augment our understanding of diseases including acute stroke and tumor. Indeed, there is currently much interest in translating CEST MRI for *in vivo* and clinical use; in order to realize these applications, however, it is necessary to enhance the sensitivity of CEST MRI (11,16,17).

CEST MRI contrast is complex. In addition to labile proton concentration and exchange rate, CEST contrast also depends on imaging parameters including magnetic field strength, RF irradiation power, duration, and scheme (5,18). These factors affect CEST contrast because, whereas it takes a reasonably strong RF power to efficiently saturate exchangeable protons, the RF pulse may also directly attenuate bulk water signal and thus reduce the CEST contrast. Both numerical and analytical solutions have been established to quantify CEST contrast and guide the design of novel sensitive CEST agents (14,18-21). For the simplistic continuous wave (CW) RF irradiation scheme, CEST MRI contrast exponentially approaches its steady state with the RF irradiation time following the apparent longitudinal relaxation rate of bulk water (22,23). Hence, the commonly used CEST MRI sequence includes a long RF irradiation module, either continuous wave (CW) or RF pulse train, followed by a fast image readout sequence such as echo planner imaging (EPI) or fast spin echo (FSE) (17,24-26). In addition, signal averaging is often needed to enhance the sensitivity of small CEST MRI contrast, prolonging the scan time. Therefore, our study aimed to develop a sensitive CEST MRI sequence with improved spatial coverage and temporal resolution.

We here proposed to unevenly segment the RF irradiation into two periods, a long primary RF pulse that introduces the steady state CEST contrast, and a repetitive short secondary RF irradiation module to lock the CEST contrast. Given that fast image acquisition typically takes only tens of milliseconds, CEST contrast should be reasonably maintained by the short secondary RF saturation pulse. Rather than repeating the long relaxation recovery and RF irradiation module, multi-slice acquisition and signal averaging can be repeated after each short secondary RF irradiation, and thereby, minimize the total scan time. We evaluated the proposed CEST MRI technique using a tissue-like pH phantom, and observed CEST contrast comparable to that obtained with a commonly used CEST MRI sequence. In addition, we examined the proposed method as a function of the secondary RF pulse duration and the imaging excitation angle, and showed that the modified sequence, once optimized, significantly improved the sensitivity of multi-slice CEST MRI. Furthermore, we applied the proposed method to image acute stroke animals, and showed that it detected ischemic lesion, similar as the conventional CEST MRI method.

2. METHODS

PHANTOM

A pH phantom was prepared using Creatine and low gelling point (LGP) agarose, as reported previously (5). Briefly, we prepared 2% agarose and phosphate buffered saline (PBS) solution (Sigma Aldrich, St Louis, MO). We microwave heated the mixture, and then immersed it in a water bath at 50°C (Cole-Parmer, Vernon Hills, IL). When the temperature of the gel solution stabilized, Creatine was added to reach 60 mM and mixed well. We then titrated the pH to 6.7 and 5.7 at 50°C (EuTech Instrument, Singapore), and transferred them to the inner and outer compartments of the dual pH phantom, respectively. The phantom was left to solidify at room temperature before the experiment.

Acute Stroke Animal Model

Animal experiments were carried out in accordance with guidelines approved by the Subcommittee on Research Animal Care at the Massachusetts General Hospital (SRAC,

MGH). Adult male Wistar rats (280-320 g, N=3) were imaged immediately after permanent filament middle cerebral artery occlusion (MCAO), while remaining under anesthesia using ~1.5% isoflurane (13). The animals' core temperature was maintained within the normal physiological range by a circulating warm water jacket positioned around the torso. In addition, animal heart rate and blood pO₂ was monitored online (Nonin Pulse Oximeter 8600, Plymouth, MN). Standard permanent middle cerebral artery occlusion (MCAO) was induced by inserting a 4-0 nylon suture into the lumen of internal carotid artery (ICA) to block the origin of the middle cerebral artery (MCA).

MRI

All images were acquired at 4.7 T (Bruker Biospec, Billerica, MA). To minimize the field inhomogeneity artifacts, we used a volume RF transmiter, and shimmed the magnetic field using Fastmap. The image matrix was 96×64 and zero-filled to 128×128 (bandwidth=150 kHz). We measured T₁ and T₂ with single-shot, single-slice EPI (slice thickness = 5 mm, field of view=48×48 mm). Specifically, the T₁ map was derived using an adiabatic inversion recovery sequence with seven inversion intervals: 0.1, 0.5, 1, 1.5, 2, 5 and 7.5 s (repetition time (TR)=12 s, echo time (TE)=47 ms, and number of average (NA)=2); the T₂ map was derived from five separate spin-echo (SE) images with echo time (TE) being 50, 60, 80, 100 and 150 ms (TR=12s and NA=2). The amine protons of Creatine at 6.6 ppm were probed for CEST imaging. In addition, we acquired five slices for CEST MRI (slice thickness =1.8 mm, slice interval =2 mm). We studied the CEST contrast as a function of the secondary RF irradiation duration and gradient echo (GE) excitation angle. Specifically,

a) Secondary RF irradiation time (TS₂)—Z-spectra were acquired with RF irradiation applied from -3 to 3 ppm (±600 Hz at 4.7T), with a frequency interval of 0.125 ppm (25 Hz), NA=2. The conventional CEST MRI sequence has a long CW RF irradiation pulse, followed by spin echo EPI (TR=12 s, TS=5 s and TE=47 ms). For the proposed fast RF-segmented GE CEST MRI, the primary RF irradiation time was also 5s (TE=23 ms). To evaluate the secondary RF irradiation pulse duration, the secondary RF irradiation time was varied from 0.5, 1, 1.5, 2 to 2.5 s; we used two RF amplitudes of 0.75 and 1.5 μT. Whereas the conventional CEST MRI uses a spin echo sequence, the modified CEST approach employs GE readout to take the advantage of short effective repetition time, with an excitation angle of 60°.

b) GE excitation angle (α)—We also evaluated the dependence of the modified CEST MRI contrast on GE excitation angle. MTR_{asym} was obtained as (I_{ref}-I_{label})/I₀, where I_{ref} and I_{label} are the reference and label scans, and I₀ is the control scan. The RF amplitude was 0.75 μT, with the excitation angle serially varied from 15° to 90°, in six steps. The conventional multi-slice SE CEST MRI was signal-averaged twice. For the proposed modified sequence, we selected a secondary irradiation time of 0.5s, and an averaging number of 8 to approximately match the total scan time. In addition, the contrast to noise ratio (CNR) was derived by calculating the mean and standard deviation (SD) of the MTR_{asym} map for each pH compartment, and computed as CNR=mean/SD.

For acute stroke animal imaging, we used a dual RF coil setup in order to achieve high sensitivity and RF field homogeneity. Single shot EPI (bandwidth= 200 kHz) was applied with its image matrix being 64×64 for a FOV of 25×25 mm. For the conventional APT MRI, we have Tr/TE=3500ms/15 ms, TS=3000ms and B₁=0.75μT (Fig. 1). The control scan was averaged 8 times (NA₁=8), while the labeling and reference scan were averaged 16 times (NA₂=16). For the proposed fast APT MRI, we have Tr/TE=3500ms/10 ms, TS₁=3000ms, TS₂=500 ms. In addition, we set NA₁=8 and NA₂=32 so that total scan time for the conventional APT and the proposed fast APT MRI was approximately equal, being about 4

minutes. In addition, diffusion weighted images were obtained with two b values of 250 and 1000 mm²/s. Furthermore, all values were reported as mean $\pm$ SD.

3. RESULTS

Figure 1 shows a commonly used fast SE-CEST MRI method along with the proposed RF irradiation-segmented GE CEST MRI pulse sequence. The conventional sequence includes three periods: relaxation recovery, RF irradiation, and fast image acquisition (Fig. 1a). It is important to note that the RF irradiation can be either continuous wave (CW) or RF pulse train (17). Using fast image acquisition, one can obtain multi-slice images after a single long RF irradiation, and the relaxation-induced loss of contrast can be corrected during post-processing (24). In comparison, the proposed sequence utilizes the long primary RF irradiation module to generate the steady state CEST contrast, and short secondary RF pulses applied immediately after each slice acquisition to maintain the steady state CEST contrast (Fig. 1b). As such, whereas magnetization recovers towards the equilibrium state during image readout, following the intrinsic longitudinal relaxation rate of bulk water (R_{1w}), the secondary RF irradiation module re-saturates the magnetization towards the steady state CEST contrast at a rate governed by the apparent longitudinal relaxation rate of bulk water (r_{1w}). Because multi-slice acquisition and signal averaging are conducted with the short secondary saturation pulse rather than with the long primary RF irradiation, its total scan time can be shown to be $t = Tr + TS_1 + NA * NS * TS_2$, where Tr is the pre-saturation delay, NA and NS being the number of averages and number of slices, with TS_1 and TS_2 being the primary and secondary RF saturation duration. In comparison, the total scan time for the conventional CEST MRI is equal to $NA * (Tr + TS_1)$. In addition, if the maximal pulse duration is limited by RF amplifier, the proposed sequence can be divided into multiple sets of averages. The total scan time will become $t = NA_2 * (Tr + TS_1 + NA_1 * NS * TS_2)$ and $NA = NA_1 * NA_2$.

Fig. 2 compares multi-slice CEST Z-spectra and MTR_{asym} obtained with both the conventional and proposed modified sequences. Specifically, Fig. 2a shows Z-spectra of the inner pH compartment, as acquired using the conventional multi-slice CEST ($B_1 = 1.5\mu T$). It is clear that longitudinal relaxation induced noticeable signal recovery (loss of contrast). Specifically, whereas the signal intensity at water resonance was 1% during acquisition of the first slice, it relaxed to about 11% when the final slice was acquired. The MTR_{asym} was found to be $10.8 \pm 0.4\%$ (mean $\pm$ SD) at 1.9 ppm from water resonance (Fig. 2b). In comparison, Z-spectra obtained using the proposed sequence nearly overlapped for all 5 slices ($TS_2 = 1$ s, Fig. 2c). In addition, the MTR_{asym} (Fig. 2d) appeared more symmetrical around the labile proton frequency. The results confirmed that although the duration of multi-slice image acquisition is relatively short, there is still significant change in the MR signal, which can be effectively compensated by the secondary RF saturation pulse. Using the modified sequence, the total acquisition time for the Z-spectrum was about 20, 18, 16, 14 and 12 min for TS_2 times of 2.5, 2, 1.5, 1 and 0.5 s, respectively, equal to or shorter than the conventional sequence (~ 20 min). The CEST contrast at 1.9 ppm was found to be $11.3 \pm 0.4\%$, slightly above that obtained with the conventional method. The fact that the modified CEST sequence showed large improvement in Z-spectra while only subtle change in MTR_{asym} was observed is likely due to the short image acquisition time (~ 60 ms per slice) relative to T_1 . Indeed, T_1 was found to be 2.59 ± 0.03 s and 2.54 ± 0.03 s, respectively, for the inner (pH=6.7) and outer (pH=5.7) compartments, while the respective T_2 of these compartments were 68 ± 8 ms and 73 ± 5 ms. Nevertheless, the significant improvement in Z-spectra and the reduction of the total scan time suggested that the modified fast multi-slice RF-segmented CEST sequence, if optimized, may indeed augment CEST MRI.

Fig. 3 shows the obtained CEST contrast as a function of the secondary RF irradiation time (TS_2). Specifically, the CEST contrast for the inner pH compartment was higher than that of the outer compartment, which is consistent with the fact that amine proton exchange is dominantly base-catalyzed (5). For the B_1 amplitude of 0.75 μ T, the CEST contrast was found to be $10.9\% + 0.3\% \cdot TS_2$, and $6.2\% - 0.04\% \cdot TS_2$ for pH of 6.7 and 5.7, respectively (Fig. 3a). A similar relationship was found for B_1 of 1.5 μ T, where CEST was measured at $11\% + 0.7\% \cdot TS_2$ and $5.4\% + 0.5\% \cdot TS_2$ (Fig. 3b). Linear regression analysis (ANOVA) showed that the dependence of CEST contrast over TS_2 is insignificant ($F > 0.05$). Hence, the CEST contrast obtained from the modified fast sequence is comparable to that obtained using the conventional method, and with significantly reduced scan time.

Given that a secondary RF irradiation pulse as short as 0.5 s may be sufficient to maintain CEST contrast for multi-slice acquisition (Fig. 3), the effective repetition time may be significantly reduced from that of the conventional CEST MRI method. Hence, to take the advantage of fast repetition time, we postulate that the GE sequence should be used, and that its excitation angle must be optimized. We repeated CEST imaging by systematically varying the RF flip angle, from 15° to 90° in six steps. Fig. 4a shows multi-slice MTR_{asym} maps obtained with the conventional sequence and the modified sequence. The CEST contrast appeared to be maximal at 15° , while its contrast-to-noise ratio (CNR) seemed to be very poor, suggesting that the imaging flip angle must be optimized such that both large CEST contrast and high CNR could be simultaneously obtained. Indeed, Fig. 4b shows that the CEST contrast was maximal at 15° , decreasing slightly with flip angle for both compartments. This change may be attributed to the fact that large flip angle significantly perturbs the CEST steady state, which may not fully recover under a short secondary RF irradiation, as used here ($TS_2 = 0.5$ s). In comparison, the CEST CNR initially increased with flip angle, peaking at around 60° , and then decreased for larger flip angles (i.e., 75° and 90° , Fig. 4c). It is important to note that the CEST MRI CNR reflects not only the CEST contrast, but also the signal-to-noise ratio (SNR) of the image. Therefore, whereas a small flip angle minimally perturbs the spin state, leading to maximal CEST contrast, image intensity is low, and hence, suffers from poor SNR. In sum, we showed that for the gel CEST phantom undergoing slow and intermediate chemical exchange, comparable CEST contrast can be obtained with either sequence, while the modified sequence significantly improved the CNR over the conventional CEST MRI sequence.

Fig. 5 shows apparent diffusion coefficient (ADC) and APT maps of a representative stroke animal, about 1 hr after MCAO. The stroke lesion appeared as hypointensity in the ADC map, which also showed reduction in MTR_{asym} maps, both the conventional and modified APT MRI. Two regions of interest (ROI) were selected in the ADC map, one in the contralateral area (cROI) and another one in the ipsilateral stroke lesion (iROI). Their ADCs were $0.73 \pm 0.05 \mu\text{m}^2/\text{ms}$ and $0.59 \pm 0.06 \mu\text{m}^2/\text{ms}$, respectively. For the conventional APT MRI, the MTR_{asym} for cROI and iROI was $-1.5\% \pm 0.8\%$ and $-3.3\% \pm 0.8\%$, while being $-1.4\% \pm 0.7\%$ and $-2.9\% \pm 0.6\%$ for the proposed method, respectively. It is important to note that whereas long CW RF irradiation is used, its average SAR for the head was estimated to be about 0.7 W/kg, assuming 100% RF duty cycle, for an RF amplitude of 0.75 μ T (27,28). This shows that for weak RF power used in our study, the energy deposition is well within the SAR limit, feasible for in vivo applications and clinical translation.

4. DISCUSSION

Our study showed that by unevenly segmenting the RF irradiation, the sensitivity of CEST MRI can be significantly improved without loss of CEST contrast. Because the maximal CEST contrast is obtained using a long RF irradiation module, following the apparent relaxation time of bulk water, it is much more time efficient to maintain the steady state

CEST contrast, once it is obtained, by applying short secondary RF irradiation for multi-slice acquisition and signal averaging. We have previously proposed an alternative multi-slice CEST MRI strategy, in which the relaxation-induced loss of CEST contrast was compensated during post-processing (24). In comparison, the newly proposed modified method does not require acquisition of a T_1 map, and hence, may be more applicable for *in vivo* use. In addition, Dixon et al. have shown that the RF irradiation can be split into multiple shorter irradiations for each slice, permitting fast multi-slice acquisition (26). Moreover, Liu et al. have proposed to adjust the RF irradiation scheme based on the image acquisition method, suggesting long RF irradiation for rapid acquisition with relaxation enhancement (RARE) and short RF irradiation for each k-space trajectory for fast low angle short (FLASH) readout (25). In comparison, our current method segmented the RF irradiation unevenly into a long primary RF irradiation module and multiple, short secondary RF irradiation periods for a multi-slice acquisition and signal averaging, which can also be adapted for imaging readouts other than EPI. Our proposed method should be particularly useful for diamagnetic CEST MRI, as the exchange rates are typically within the slow and intermediate exchange regime, and a long RF irradiation pulse is required for maximal CEST contrast. Our observations that the multi-slice Z-spectra obtained using the modified sequence showed significant improvement, and that the optimal CNR was nearly double that of the conventional sequence, suggested that the newly proposed method might be helpful for the endogenous pH-weighted APT MRI, whose contrast is typically only a few percent. Furthermore, the modified method also enables one to use lipid suppression and outer volume suppression modules immediately before each image acquisition, to minimize potential imaging artifacts(29).

Given that a relatively brief secondary irradiation pulse (e.g., 0.5 s) is sufficient to maintain the steady state CEST contrast, a GE sequence should be selected in order to take advantage of significantly reduced effective repetition time. In addition, imaging pulses (RF and gradient) cause negligible change in CEST contrast, likely because the imaging pulses were too short to induce noticeable saturation transfer contrast. It is worth noting that the proposed fast RF irradiation-segmented CEST MRI method has multiple parameters to optimize, including the secondary RF amplitude/power, duration, and excitation flip angle. We have shown that the maximal CEST contrast is obtained with a small RF flip angle, and yet, CNR is significantly higher at a moderate RF flip angle to compromise the CEST contrast and image SNR. Nevertheless, when optimized, our data show that the modified CEST MRI method can significantly improve the sensitivity of CEST imaging.

Whereas we used CW RF irradiation pulse for both the primary and secondary RF irradiation, a shaped RF pulse train can be applied for CEST MRI (17). It is important to note that if an extremely short secondary RF pulse duration is chosen, the RF sideband excitation may become noticeable, and hence, should be avoided. In our study, the shortest secondary RF irradiation duration we used was 0.5 s, which is reasonably long and sufficient for maintaining the steady state CEST contrast. Although we used long CW RF irradiation pulse, its RF energy deposition was quite small due to its relatively weak RF amplitude, well below the specific absorption rate (SAR) limit.

5. CONCLUSIONS

Our study modified the conventional CEST MRI sequence by dividing the RF irradiation unevenly into two segments, a long primary RF irradiation to generate the steady state CEST MRI contrast, and repeated short secondary RF irradiation to maintain the CEST contrast for multi-slice acquisition and signal averaging. We evaluated the modified fast multi-slice RF-segmented CEST MRI using a tissue-like dual-pH phantom, and showed that its CEST contrast was similar to that of the conventional CEST MRI method, yet with significantly

improved sensitivity per time. We also demonstrated that the proposed sequence can detect ischemic lesion during acute stroke, similar as the conventional CEST MRI sequence, and suitable for in vivo applications.

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REFERENCES

1. Ward KM, Balaban RS. Determination of pH using water protons and chemical exchange dependent saturation transfer (CEST). *Magn Reson Med*. 2000; 44:799–802. [PubMed: 11064415]
2. Goffeney N, Bulte JWM, Duyn J, Bryant LH, van Zijl PCM. Sensitive NMR detection of cationic-polymer-based gene delivery systems using saturation transfer via proton exchange. *J Am Chem Soc*. 2001; 123:8628–8629. [PubMed: 11525684]
3. Aime S, Delli CD, Terreno E. Highly sensitive MRI chemical exchange saturation transfer agents using liposomes. *Angew Chem Int Ed Engl*. 2005; 44(34):5513–5515. [PubMed: 16052647]
4. Sherry AD, Woods M. Chemical Exchange Saturation Transfer Contrast Agents for Magnetic Resonance Imaging. *Annu Rev Biomed Eng*. 2008; 10:391–411. [PubMed: 18647117]
5. Sun PZ, Sorensen AG. Imaging pH using the Chemical Exchange Saturation Transfer (CEST) MRI: Correction of Concomitant RF Irradiation Effects to Quantify CEST MRI for Chemical Exchange Rate and pH. *Magn Reson Med*. 2008; 60(2):390–397. [PubMed: 18666128]
6. van Zijl PCM, Jones CK, Ren J, Malloy CR, Sherry AD. MRI detection of glycogen in vivo by using chemical exchange saturation transfer imaging (glycoCEST). *Proc Natl Acad Sci*. 2007; 104(11):4359–4364. [PubMed: 17360529]
7. Gilad AA, McMahon MT, Walczak P, Winnard PT Jr. Raman V, van Laarhoven HW, Skoglund CM, Bulte JW, van Zijl PC. Artificial reporter gene providing MRI contrast based on proton exchange. *Nat Biotechnol*. 2007; 25(2):217–219. [PubMed: 17259977]
8. Vinogradov E, He H, Lubag A, Balschi JA, Sherry AD, Lenkinski RE. MRI detection of paramagnetic chemical exchange effects in mice kidneys in vivo. *Magn Reson Med*. 2007; 58(4):650–655. [PubMed: 17899603]
9. Ling W, Regatte RR, Navon G, Jerschow A. Assessment of glycosaminoglycan concentration in vivo by chemical exchange-dependent saturation transfer (gagCEST). *Proc Natl Acad Sci*. 2008; 105(7):2266–2270. [PubMed: 18268341]
10. Vasalatiy O, Gerard RD, Zhao P, Sun X, Sherry AD. Labeling of Adenovirus Particles with PARACEST Agents. *Bioconjug Chem*. 2008; 19(3):598–606. [PubMed: 18254605]
11. Mougin OE, Coxon RC, Pitiot A, Gowland PA. Magnetization transfer phenomenon in the human brain at 7 T. *NeuroImage*. 2010; 49(1):272–281. [PubMed: 19683581]
12. Zhou J, Payen J, Wilson DA, Traystman RJ, van Zijl PCM. Using the amide proton signals of intracellular proteins and peptides to detect pH effects in MRI. *Nat Med*. 2003; 9:1085–1090. [PubMed: 12872167]
13. Sun PZ, Zhou J, Sun W, Huang J, van Zijl PCM. Detection of the ischemic penumbra using pH-weighted MRI. *J Cereb Blood Flow Metab*. 2007; 27(6):1129–1136. [PubMed: 17133226]
14. Sun PZ, Zhou J, Huang J, van Zijl P. Simplified Quantitative Description of Amide Proton Transfer (APT) Imaging During Acute Ischemia. *Magn Reson Med*. 2007; 57(2):405–410. [PubMed: 17260362]
15. Jokivarsi KT, Gröhn HI, Gröhn OH, Kauppinen RA. Proton transfer ratio, lactate, and intracellular pH in acute cerebral ischemia. *Magn Reson Med*. 2007; 57(4):647–653. [PubMed: 17390356]
16. Jones CK, Schlosser MJ, van Zijl PCM, Pomper GM, Golay X, Zhou J. Amide proton transfer imaging of human brain tumors at 3T. *Magn Reson Med*. 2006; 56(3):585–592. [PubMed: 16892186]

17. Sun PZ, Benner T, Kumar A, Sorensen AG. An Investigation of Optimizing and Translating pH-Sensitive Pulsed-Chemical Exchange Saturation Transfer (CEST) Imaging to a 3 T Clinical Scanner. *Magn Reson Med*. 2008; 60(4):834–841. [PubMed: 18816867]
18. Sun PZ, van Zijl PCM, Zhou J. Optimization of the irradiation power in chemical exchange dependent saturation transfer experiments. *J Magn Reson*. 2005; 175(2):193–200. [PubMed: 15893487]
19. Woessner DE, Zhang S, Merritt ME, Sherry AD. Numerical solution of the Bloch equations provides insights into the optimum design of PARACEST agents for MRI. *Magn Reson Med*. 2005; 53(4):790–799. [PubMed: 15799055]
20. Li AX, Hudson RHE, Barrett JW, Johns CK, Pasternak SH, Bartha R. Four-pool modeling of proton exchange processes in biological systems in the presence of MRI-paramagnetic chemical exchange saturation transfer (PARACEST) agents. *Magn Reson Med*. 2008; 60(5):1197–1206. [PubMed: 18958857]
21. Sun PZ. Simplified and scalable numerical solution for describing multi-pool chemical exchange saturation transfer (CEST) MRI contrast. *J Magn Reson*. 2010; 205(2):235–241. [PubMed: 20570196]
22. Zhou J, Wilson DA, Sun PZ, Klaus JA, van Zijl PCM. Quantitative description of proton exchange processes between water and endogenous and exogenous agents for WEX, CEST, and APT experiments. *Magn Reson Med*. 2004; 51:945–952. [PubMed: 15122676]
23. McMahon M, Gilad A, Zhou J, Sun PZ, Bulte J, van Zijl PC. Quantifying exchange rates in chemical exchange saturation transfer agents using the saturation time and saturation power dependencies of the magnetization transfer effect on the magnetic resonance imaging signal (QUEST and QUESP): Ph calibration for poly-L-lysine and a starburst dendrimer. *Magn Reson Med*. 2006; 55(4):836–847. [PubMed: 16506187]
24. Sun PZ, Murata Y, Lu J, Wang X, Lo EH, Sorensen AG. Relaxation-compensated fast multi-slice amide proton transfer (APT) imaging of acute ischemia. *Magn Reson Med*. 2008; 59(5):1175–1182. [PubMed: 18429031]
25. Liu G, Ali MM, Yoo B, Griswold M, Tkach J, Pagel M, D. PARACEST MRI with improved temporal resolution. *Magn Reson Med*. 2009; 61(2):399–408. [PubMed: 19165903]
26. Dixon TW, Hancu I, Ratnakar SJ, Sherry DA, Lenkinski RE, Alsop DC. A multislice gradient echo pulse sequence for CEST imaging. *Magn Reson Med*. 2010; 63(1):253–256. [PubMed: 19918889]
27. Wang Y, Grist T, Mistretta C. Dispersion in magnetization transfer contrast at a given specific absorption rate due to variations of RF pulse parameters in the magnetization transfer preparation. *Magn Reson Med*. 1997; 37(6):957–962. [PubMed: 9178249]
28. Collins C, Li S, Smith M, B. SAR and B1 field distributions in a heterogeneous human head model within a birdcage coil. *Magn Reson Med*. 1998; 40(6):847–856. [PubMed: 9840829]
29. Sun PZ, Zhou J, Sun W, Huang J, van Zijl PCM. Suppression of lipid artifacts in amide proton transfer imaging. *Magn Reson Med*. 2005; 54(1):222–225. [PubMed: 15968669]

Fig. 1.

Comparison of the conventional and the proposed CEST MRI sequences. The conventional CEST MRI sequence often includes a long relaxation delay and RF irradiation (CW or pulse train), followed by fast image readout (Fig. 1 a). The sequence is repeated for each signal average and RF offset. By comparison, the modified CEST sequence segments the RF irradiation into a primary long module to generate the steady state CEST contrast, and repetitive short secondary RF irradiation to maintain the contrast for multi-slice acquisition and signal average (Fig. 1 b). As such, the long relaxation recovery and primary RF irradiation module is repeated only when the RF offset is varied, thereby, significantly reducing the scan time.

Fig. 2.

Comparison of CEST MRI obtained with the conventional and modified sequences. Z-spectra and MTR_{asym} were obtained with the conventional CEST MRI (a and b) and those obtained using the proposed RF-segmented GE CEST MRI sequence (c and d). Whereas relaxation induced significant recovery in the Z-spectra obtained with the conventional sequence, resulting in noticeable deviation in the multi-slice signal (a), such artifact was well suppressed with the modified sequence (c), and the MTR_{asym} appeared to be more symmetric around the labile proton offset (d vs b).

Fig. 3.

Dependence of CEST contrast (mean $\pm$ S.D.) as a function of TS_2 . CEST contrast obtained with conventional sequence was shown in gray. The CEST contrast showed very little change with TS_2 for both pH compartments, suggesting that the short secondary saturation pulse is efficient to maintain the CEST contrast for fast multi-slice acquisition.

Fig. 4.

Evaluation of the CEST MRI contrast as a function of the GE excitation angle. a) Multi-slice MTR_{asym} map (± 1.9 ppm) obtained using the conventional SE CEST MRI and the modified fast GE CEST MRI with the excitation angle varied from 15°, 60° and 90°. Whereas the CEST contrast was highest at 15°, its contrast-to-noise ratio (CNR) was poor. b) CEST contrast using the modified sequence decreased slightly with imaging RF flip angle for both pH compartments, with the CEST MRI contrast difference shown in blue squares. c) The SNR of CEST contrast initially increased with flip angle, peaked around 60°, and subsequently decreased. The maximal SNR nearly doubled that obtained with conventional CEST MRI sequence.

Fig. 5.

Diffusion and pH-weighted endogenous APT MRI of a representative acute stroke animal.

a) Ischemic lesion appeared as hypointensity in the ADC map. Two ROIs were manually drawn in a representative slice for lesion analysis. b) pH-weighted APT MRI with the conventional and proposed CEST MRI sequence showed similar deficit in the ischemic lesion, suggesting the feasibility of in vivo application of the proposed sequence.