Published in final edited form as:

Magn Reson Med. 2011 October ; 66(4): 1042–1048. doi:10.1002/mrm.22894.

Simulation and optimization of pulsed radio frequency (RF) irradiation scheme for chemical exchange saturation transfer (CEST) MRI – demonstration of pH-weighted pulsed-amide proton CEST MRI in an animal model of acute cerebral ischemia

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Abstract

Chemical exchange saturation transfer (CEST) MRI is capable of measuring dilute labile protons and microenvironment properties; however, the CEST contrast is also dependent upon experimental conditions, particularly, the RF irradiation scheme. Although continuous-wave (CW) RF irradiation has been conventionally utilized, the RF pulse duration or duty cycle are limited on most clinical systems, for which pulsed RF irradiation must be chosen. Here, conventional numerical simulation was extended to describe pulsed-CEST MRI contrast as a function of RF pulse parameters (i.e., RF pulse duration and flip angle) and labile proton properties (i.e., exchange rate and chemical shift). For diamagnetic CEST agents undergoing slow/intermediate chemical exchange, our simulation showed a linear regression relationship between the optimal mean RF power for pulsed-CEST MRI and that of CW-CEST MRI. Worth noting, the optimized pulsed-CEST contrast was approximately equal to that of CW-CEST MRI for exchange rates below 50 s⁻¹, as confirmed experimentally using a multi-compartment pH phantom. Moreover, acute stroke animals were imaged with both pulsed- and CW- amide protons CEST MRI, which showed similar contrast. In summary, our study elucidated the RF irradiation dependence of pulsed-CEST MRI contrast, providing useful insights to guide its experimental optimization and quantification.

Keywords

amide proton transfer (APT); chemical exchange saturation transfer (CEST); pH; radio frequency (RF); stroke

1. INTRODUCTION

Chemical exchange saturation transfer (CEST) imaging is an emerging MRI technique capable of detecting dilute labile proton groups and microenvironment properties such as pH and temperature (1–3). For exchangeable proton groups undergoing slow and intermediate chemical exchange with bulk water protons, CEST contrast is nearly proportional to the

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labile proton concentration (f) and exchange rate (k_{sw}), and therefore provides sizeable sensitivity enhancement for detecting dilute CEST agents (4,5). For instance, it has been shown that certain polypeptides and metabolites may be detected via CEST MRI (6–9). In addition, CEST MRI has been increasingly explored for in vivo applications (10–12). Importantly, amide proton transfer (APT) imaging, a specific form of CEST MRI that probes the amide proton chemical exchange, is sensitive to local pH (13,14). As such, endogenous APT MRI has been increasingly used for imaging ischemic acidosis, particularly useful for characterizing impaired tissue metabolism during acute stroke, complementary to the commonly used perfusion and diffusion MRI (15–18).

However, CEST MRI contrast is complex. In addition to labile proton concentration and exchange rate, the measureable CEST contrast also depends on experimental parameters such as magnetic field strength, RF irradiation power/amplitude, duration and scheme (19). More specifically, RF irradiation may not only saturate labile protons but also directly attenuate the bulk water signal (spillover), reducing the sensitivity and specificity of CEST MRI. Conventionally, CEST imaging has been implemented using fast image readout with a long continuous-wave (CW) RF irradiation after sufficient relaxation recovery, such that the steady state CEST contrast is obtained. In fact, mathematical solutions previously developed were mainly for CW-CEST MRI (19–23). On the other hand, CW RF irradiation may not be applicable on systems where the maximal RF pulse duration and duty cycle are limited, particularly on clinical scanners, for which, the pulsed RF irradiation scheme must be applied instead (24–27). Consequently, it is crucial to quantify and optimize pulsed-CEST MRI for in vivo applications.

For CW-CEST MRI, it has been shown that experimentally obtainable CEST contrast peaks at an optimal RF amplitude, under which the saturation efficiency and RF spillover factor are balanced (19). The goal of our study is to establish a quantitative algorithm to describe pulsed-CEST MRI. It is important to point out that whereas there is a single parameter to optimize for CW-CEST MRI (i.e., RF amplitude), multiple variables must be evaluated for pulsed-CEST MRI, including RF flip angle and pulse duration (Fig. 1). Because the transient solution is tedious and complex, our study modified the numerical solution, previously developed for CW-CEST MRI, to describe the pulsed-CEST MRI contrast (28,29). Specifically, we simulated pulsed-CEST MRI as a function of RF pulse train parameters (RF flip angle and duration) and CEST agent properties (exchange rate and chemical shift), assuming a commonly used Gaussian-shaped RF pulse. In addition, we compared the optimal equivalent RF power for pulsed-CEST MRI with that of CW-CEST MRI, and the simulation was validated with a multi-compartment pH phantom. Furthermore, pH-weighted endogenous APT MRI was obtained with both pulsed- and CW-CEST MRI sequence, which showed similar contrast, consistent with simulation and phantom results.

2. MATERIALS AND METHODS

Numerical Simulation

We simulated pulsed- and CW- CEST MRI in Matlab (MathWorks, Natick, MA) with modified Bloch-McConnell solution (20,21). Specifically, pulsed-CEST MRI was simulated piecewise for each repetition of RF pulse and interpulse delay. Each RF pulse was divided into 64 steps and the spin evolution within each step ($\Delta\tau = \tau_p/64$) was modeled assuming a

constant B_1 amplitude, $B_1(i)|_{i=1:N} = \frac{\phi}{\gamma} \cdot \frac{e^{-(i \cdot \tau_p/N - \tau_p/2)^2/c^2}}{\sum_{i=1:N} e^{-(i \cdot \tau_p/N - \tau_p/2)^2/c^2} \cdot \frac{\tau_p}{N}}$, where γ is the gyromagnetic ratio, ϕ is RF flip angle, and $c = \frac{\tau_p}{2\sqrt{-\ln(tl)}}$ with tl being the truncation level, chosen to be 1%.

In addition, transverse magnetization was set to zero immediately before inter-pulse delay to represent the dephasing caused by crusher gradients, while its longitudinal magnetization relaxes towards its equilibrium state. The magnetization at the end of inter-pulse delay was then used as the initial state for iterated simulation till the end of RF pulse train. Moreover, we used representative relaxation parameters, with T_1 and T_2 of 3 s and 100 ms, respectively, for bulk water, and 1 s and 15 ms for the labile proton group. The labile proton concentration with respect to bulk water protons was 1:500. Finally, we assumed a total RF saturation time (TS) of 3 s and duty cycle of 50%, for a magnetic field strength of 4.7T.

RF pulse flip angle (Fig. 2)—Z-spectra were simulation for representative flip angles of 90° , 180° , 360° and 450° , assuming a commonly used Gaussian shaped pulse and a typical pulse duration of 15 ms. The chemical shift was varied from -5 to 5 ppm with intervals of 0.125 ppm. In addition, CEST contrast was solved as a function of RF flip angle, for three representative exchange rates: 25 , 50 and 100 s^{-1} . Moreover, the RF flip angle (ϕ) was varied from 150° to 250° with intervals of 10° , assuming a representative pulse duration of 15 ms and the optimal flip angle was solved as a function of exchange rate, for three typical chemical shifts. Finally, the optimal flip angle was evaluated as a function of chemical shift, from 1 to 5 ppm per 0.25 ppm, for three exchange rates, 25 , 50 and 100 s^{-1} .

RF pulse duration (Fig. 3)—Z-spectra were simulation for pulse duration of 5 , 15 and 30 ms, assuming a commonly used Gaussian shaped pulse with a flip angle of 180° , and the chemical shift was varied from -5 to 5 ppm with intervals of 0.125 ppm. In addition, CEST contrast was solved as a function of RF pulse duration, for three representative exchange rates of 25 , 50 and 100 s^{-1} . Moreover, the RF pulse duration was increased stepwise from 5 to 30 ms, with intervals of 1 ms and the optimal pulse duration was solved as a function of exchange rate for three typical chemical shift, 1.9 , 3.5 and 5 ppm. Finally, the optimal pulse duration was evaluated as a function of chemical shift, from 1 to 5 ppm per 0.25 ppm, for three representative exchange rates, 25 , 50 and 100 s^{-1} .

Optimal RF flip angle and pulse duration (Fig. 4)—Both CW- and pulsed-CEST MRI were simulated with the exchange rate varied from 10 to 100 s^{-1} , at intervals of 5 s^{-1} , for three representative chemical shifts of 1.9 , 3.5 and 5 ppm. For each exchange rate and chemical shift, we used 2-dimensional variants of the RF flip angle and pulse duration: 150° to 250° with an interval of 10° , and 5 to 25 ms with an interval of 1 ms, respectively.

Phantom

We prepared a pH phantom using creatine and low gelling point (LGP) agarose, as reported previously (14,27). In short, we added 1% agarose into phosphate-buffered saline (PBS) solution, doped with a trace amount of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (Sigma Aldrich, St Louis, MO). The mixture was microwave heated, and then immersed into a water bath at 50°C (Cole-Parmer, Vernon Hills, IL). When the temperature of the gel solution stabilized, we added creatine and mixed well until a final concentration of 50 mM . We serially titrated the pH of the creatine-gel solution to 5.5 , 6 , 6.25 , 6.5 , 6.75 and 7 at 50°C (EuTech Instrument, Singapore), and separately transferred the solution into multiple centrifuge tubes. The tubes were immediately sealed and inserted into a tight-fitting phantom holder, filled with 1% agarose PBS solution to minimize susceptibility mismatch. It is important to note that whereas the phantom pH at room temperature may be slightly different from values titrated at 50°C , the pH contrast remains among pH compartments and is suitable for evaluating pH-weighted CEST contrast (14).

MRI

Fig 1 illustrates a typical CEST MRI sequence, which includes a long RF saturation period followed by image acquisition. Under a long RF irradiation, the CW-CEST MRI contrast is at its steady state and the only variable is the RF amplitude/power (ω_1). In comparison, pulsed RF irradiation scheme is complex, with multiple parameters to optimize, including pulse shape, flip angle (ϕ), duration (τ_p) and interpulse delay (τ_d). In addition, crusher gradients are often applied between pulses to suppress residual transverse magnetization. As Gaussian pulse is widely used, and has been previously explored for CEST MRI (13,18), our current study focused on Gaussian pulsed-CEST MRI. In addition, we studied a representative RF duty cycle of 50%, namely $\tau_p = \tau_d$ (26).

All images were acquired at 4.7 T (Bruker Biospec, Billerica, MA), which is capable of performing both CW and pulsed RF irradiation. We used single-shot single-slice echo planner image (EPI) as image readout (slice thickness = 10 mm, field of view (FOV) = 76×76 mm, bandwidth=200 kHz). The image matrix was 64×64 , and the repetition time (TR) and echo time (TE) were 10 s and 28 ms, respectively, and the RF saturation time (TS) of 5 s (NA=2). We probed creatine amine labile protons at 6.6 ppm (1.9 ppm from bulk water resonance) for CEST MRI. For CW-CEST MRI, the RF amplitude was varied from 0.75, 1, 1.25, 1.5 and 2 μ T. For pulsed-CEST MRI, the RF pulse duration was varied from 10, 15, 20, 25 to 30 ms, and for each pulse duration, the flip angle was varied from 90° to 540° , with an interval of 45° . The CEST contrast was calculated as CEST asymmetry $CESTR_{asym} = (I_{ref} - I_{label})/I_0$, where I_{ref} and I_{label} are reference and saturation scans, and I_0 is the control scan without CEST RF irradiation. In addition, B_1 field was calibrated with a 1 ms RF pre-pulse, whose flip angle (θ) was varied from 10° to 180° with an interval of 10° , and the image intensity was solved by fitting $I(\theta) = I_0 \cdot |\cos\gamma(\eta B_1 + \Delta B_1)\tau|$, where η and ΔB_1 are the scaling factor and shift of B_1 field, respectively. We found $\eta=0.95$ and $\Delta B_1 \approx 0$.

All animal experiments were carried out in accordance with guidelines approved by the Subcommittee on Research Animal Care of the Massachusetts General Hospital (SRAC, MGH). Standard filament middle cerebral artery occlusion (MCAO) was induced in anesthetized adult male Wistar rats ($n=3$, Charles River, Wilmington, MA), with both heart rate and blood SpO_2 monitored online (Nonin Pulse Oximeter 8600, Plymouth, MN). In addition, body temperature was maintained within the normal physiological range with a circulating warm water jacket positioned above the torso. Multislice MRI (5 slices, slice thickness/gap = 1.8/0.2 mm, field of view = 25×25 mm², acquisition matrix = 64×64) was obtained with single-shot echo-planar imaging (EPI) (receiver bandwidth = 200 kHz). Endogenous APT MRI was obtained using unevenly segmented RF irradiation scheme (Tr/TE/TS1/TS2=5000/15/4500/500ms), with both CW- and pulsed- CEST MRI (30). For APT MRI with CW-CEST acquisition, we had $B_1=0.75$ μ T (17), while for the pulsed-CEST MRI, we used $\tau=15$ ms and $\phi=180^\circ$. In addition, RF irradiation was applied at ± 3.5 ppm (700 Hz at 4.7T) and CEST asymmetry was calculated. Moreover, isotropic diffusion weighted MRI was obtained with two b values (250 and 1,000 mm²/s, TR/TE=3250/54ms, NA=16), and apparent diffusion coefficient (ADC) was solved by least square fitting.

3. RESULTS

We evaluated pulsed-CEST MRI contrast as a function of RF pulse flip angle. Fig. 2a shows four simulated Z-spectra, with the RF flip angle being 90° , 180° , 360° and 540° , assuming an RF pulse duration of 15 ms. These results show that whereas prominent CEST contrast can be observed with moderate flip angles (90° and 180°), the contrast decreases significantly at larger flip angles such as 360° and 540° , likely due to concomitant RF spillover effect. It is important to note that the water signal on resonance with RF saturation deviated from zero at the 360° flip angle because the RF pulse restores the bulk water

magnetization along the Z-axis before the crusher gradient. Fig. 2b shows that for three representative exchange rates of 25, 50 and 100 s⁻¹. The pulsed-CEST MRI contrast peaks when the RF flip angle is about 180–220°, but it bottoms out when the flip angle is beyond 360°. We solved the optimal RF flip angle for a typical range of exchange rate from 10 to 100 s⁻¹. Fig. 2c shows that the optimal flip angle increases slightly with the exchange rate, and similarly, with chemical shift (Fig. 2d).

We further evaluated how the pulsed-CEST MRI contrast varies with the RF pulse duration, for a representative RF flip angle of 180°. Fig. 3a shows three Z-spectra for RF pulse durations of 5, 15 and 30 ms. It is worth pointing out that the RF saturation bandwidth is significantly broadened at short pulse duration, which results in greatly attenuated signal intensity around the bulk water resonance. Fig. 3b shows pulsed-CEST contrast as a function of RF pulse duration for three representative exchange rates of 25, 50 and 100 s⁻¹. The optimal RF duration is prolonged at slower exchange rate, suggesting lower RF amplitude, similar to findings from CW-CEST MRI studies (19). We also evaluated how the optimal RF duration varies with exchange rate and chemical shift. Our results showed that the optimal RF pulse duration shortens with both exchange rate (Fig. 3c) and chemical shift (Fig. 3d). This is expected given that for the same RF flip angle (i.e., 180°), the equivalent RF power/amplitude is higher at shorter RF duration, and hence, is suitable for imaging CEST agents of higher exchange rate and larger chemical shift. Given that RF bandwidth is associated with the pulse duration, our results suggest that the optimal RF bandwidth also varies with exchange rate and chemical shift. Specifically, the bandwidth is 1610 Hz for a 1 ms Gaussian inversion pulse (RF Shape tool, Bruker Biospin, Billerica MA), which allows conversion of the optimal RF duration into RF bandwidth.

We also compared the pulsed-CEST contrast with the more commonly used CW-CEST MRI. Fig. 4a shows that for a representative chemical exchange rate range from 10 to 100 s⁻¹, the CW-CEST contrast is approximately equal to or higher than the pulsed-CEST contrast. We plotted the difference between pulsed-CEST and CW-CEST contrast as a function of exchange rate, which showed that the pulsed-CEST MRI became less effective than CW-CEST MRI, particularly at higher exchange rate. In addition, the loss of contrast is greater at higher chemical shift (Fig. 4b). Fig. 4c shows the optimal RF amplitude for the CW-CEST MRI increases with exchange rate for three representative chemical shifts, consistent with the notion that larger RF power is needed to efficiently saturate faster exchange. In addition, the equivalent RF amplitude of pulsed-CEST MRI is calculated as $\bar{B}_1 = \phi/(\gamma\tau_p)$. Fig. 4d compares the equivalent RF amplitude of pulsed-CEST MRI with that of CW-CEST MRI. Importantly, the RF amplitude for pulsed-CEST MRI displayed an excellent polynomial relationship with that of CW-CEST MRI, found to be

$B_{1_pulse_opt} \approx 0.28 * B_{1_cw_opt}^2 + 1.04 * B_{1_cw_opt}$. This linear regression relationship allows estimation of the optimal pulsed-CEST MRI parameter based on the better-understood CW-CEST MRI.

We validated the simulation using a creatine-gel phantom with serially titrated pH, whose chemical exchange rate covers a representative range of diamagnetic CEST agents (Fig. 5a). CEST MRI indeed detected the difference in pH among the compartments, as per the CW-CEST and pulsed-CEST MRI shown in Figs. 5b and 5c, respectively. For CW-CEST MRI, the RF amplitude is 1.25 μT, while for the pulsed-CEST MRI, we used an RF flip angle of 257° (after RF field calibration) and pulse duration of 20 ms. It is important to note that pulsed-CEST MRI showed noticeably lower contrast than the CW-CEST MRI, particularly for higher exchange rates/pH. Fig. 5d shows that pulsed-CEST contrast initially increased with RF flip angle, but decreased after peaking around an intermediate flip angle. Similarly, pulsed-CEST MRI contrast increased with pulse duration, but decreased when pulse duration became too long (Fig. 5e). Fig. 5f shows a 2-D histogram of optimal RF flip angle

and pulse duration for all six pH compartments, and optimal flip angle and pulse duration were found to be approximately 257° (after RF field calibration) and 20 ms, respectively. The optimal flip angle was slightly larger than that estimated from simulation (Fig. 2c), likely caused by the relatively coarse intervals of pulse flip angle and duration. In addition, the chemical exchange rate can be estimated using a previously calibrated formula for base-catalyzed creatine amine proton exchange (Fig. 5g) (14). Fig. 5h showed that CW-CEST contrast increases approximately linearly with exchange rate, suggesting excellent pH response. In comparison, whereas the pulsed-CEST MRI contrast was approximately equal to that obtained with CW-CEST MRI for exchange rates below 50 s^{-1} , it became significantly less than the CW-CEST contrast at higher exchange rates/pH (Fig. 5i). The difference in CEST contrast between pulsed-CEST and CW-CEST MRI was evaluated as $\Delta\text{CESTR} = \text{CESTR}_{\text{pulse}} - \text{CESTR}_{\text{cw}}$, which showed sizeable loss of contrast for exchange rates above 50 s^{-1} , as predicted in Fig. 4.

Finally, we evaluated pH-weighted endogenous APT MRI with both pulsed- and CW-CEST MRI sequences, using acute ischemic stroke animals. Ischemic lesion can be appreciated as hypointensity in ADC (Fig. 6a), CW- (Fig. 6b, $B_1=0.75 \mu\text{T}$) and pulsed-APT (Fig. 6c, $\tau=15 \text{ ms}$ and $\phi=180^\circ$) images, from a representative coronal slice. A region of interest (ROI) was manually selected in the striatum region based on ADC decrease, being $0.47 \pm 0.08 \mu\text{m}^2/\text{ms}$. Its APT contrast was found to be $-6.4 \pm 1.4\%$ (mean $\pm$ S.D.) and $-5.9 \pm 1.2\%$, for pulsed- and CW-CEST acquisitions, respectively. Whereas the pulsed-APT is slightly lower than that of CW-APT MRI, it provides reasonably clear depiction of ischemic lesion, and therefore serves as a viable alternative for MRI systems unable to operate CW RF irradiation.

4. DISCUSSION

Our study developed numerical simulation to elucidate pulsed-CEST MRI. We showed that whereas the optimal experimental conditions for RF flip angle and duration vary with chemical shift and exchange rate, they can be reasonably estimated based on the better-understood CW-CEST MRI. Specifically, for typical chemical shift ($< 5 \text{ ppm}$) and slow exchange rate, the optimal RF flip angle is approximately 180° , and the RF pulse duration can be derived from the optimal mean RF amplitude for pulsed-CEST MRI based on a linear regression relationship with that of CW-CEST MRI. Moreover, our study simulated CEST MRI for a range of chemical shifts (i.e., 1–5 ppm) assuming a typical field strength of 4.7T; the results we obtained can be easily extended to other field strengths such as 3T. For instance, the creatine amine proton chemical shift (1.9 ppm) was 380 Hz at 4.7T, similar to the composite amide proton chemical shift (3.5 ppm) of 450 Hz at 3T. It is necessary to point out that optimization of pulsed-CEST MRI with numerical simulation is very time-consuming given that the RF saturation scheme must be simulated piecewise; the results shown in Fig. 4 took over 10 hours on a Dell Precision T7400 Desktop due to multi-dimensional nature of the simulation (involving variable exchange rate, chemical shift, RF flip angle and duration). Therefore, by elucidating the relationship between pulsed- and CW-CEST MRI, our study has enabled reasonable estimation of the optimal pulsed RF saturation scheme, which may effectively guide experimental optimization.

It is very interesting to observe the linear regression relationship between the mean RF amplitude of pulsed-CEST MRI and that of CW-CEST MRI. For a representative CW RF amplitude of $1 \mu\text{T}$, the equivalent B_1 amplitude for optimal pulsed-CEST MRI will be $1.34 \mu\text{T}$. Given a typical RF duty cycle of 50%, the ratio between the flip angle of pulsed-CEST MRI and CW-CEST MRI within a repetition of RF pulse irradiation and interpulse delay was 67%. However, the ratio between pulsed- and CW-CEST MRI RF irradiation power can

be estimated using $p = \frac{\tau_p + \tau_d}{\int_{t=0}^{\tau_p + \tau_d} B_1^2(t) dt}$, which by our calculation yielded 211%. As such, the optimal pulsed-CEST experimental condition seems to compromise between RF amplitude and power, which indicates that the contrast mechanism of pulsed-CEST MRI is complex and before an exact analytical solution can be obtained, it is necessary to optimize it numerically. Whereas CEST contrast varies strongly with bulk water T_1 , the optimal RF power showed very little T_1 dependence (data not shown). This is not surprising since the optimal RF power depends on the competition of labeling coefficient and spillover factor. In addition, although bulk water T_2 may influence the RF spillover effect, our simulation found that it has relatively small effect upon the optimal RF power, for moderate chemical shifts. Nevertheless, our results showed that the optimal pulsed-CEST MRI condition can be reasonably estimated from that of better understood CW-CEST MRI, which may help guide experimental optimization.

Our study showed that although the pulsed-CEST MRI contrast is persistently lower than that of optimized CW-CEST MRI due to the less-efficient saturation efficiency and loss of CEST contrast during the interpulse delay, pulsed-CEST MRI provided comparable contrast for an exchange rate less than 50 s^{-1} . This observation is encouraging for clinical translation of pH-weighted APT MRI. Specifically, the endogenous amide proton exchange rate has been estimated to be about 30 s^{-1} , and therefore, is suitable for pulsed-APT MRI (13). While on the other hand, it is important to point out that pulsed-CEST MRI may not be optimal for imaging CEST agents of higher exchange rate such as certain paramagnetic CEST (PARACEST) agents (31,32). To address this limitation, we need to either implement CW-RF irradiation or design novel RF irradiation scheme. Moreover, although our study evaluated Gaussian shaped RF pulse, which has been commonly used due to its simplicity and smooth frequency profile, the algorithm we developed can be readily extended to investigate RF pulse of a given shape for pulsed-CEST MRI (13,18). Indeed, we also evaluated block and sinc RF pulses, both of which are less effective than Gaussian shaped RF pulses. Specifically, block RF pulse induces a periodic oscillation pattern in Z-spectrum due to its sidelobes in the frequency domain. For the sinc RF pulse we simulated, its peak power is significantly higher than that of Gaussian or block pulses, thereby, more susceptible to RF spillover effects. Therefore, our results suggest that the frequency spectrum of the irradiation pulse should be reasonably smooth yet narrow for pulsed-CEST MRI. Whereas we can not be exhaustive in evaluating all commonly used RF pulse shapes, our study showed that for imaging of diamagnetic CEST agents undergoing slow/intermediate chemical exchange, pulsed-CEST MRI with optimized Gaussian RF irradiation provides similar contrast as CW-CEST MRI.

5. CONCLUSIONS

Our study developed a numerical method and elucidated the pulsed-CEST MRI contrast. We showed that the optimal RF irradiation scheme for pulsed-CEST MRI can be reasonably estimated from the better-understood CW-CEST MRI, which greatly simplifies numerical optimization and experimental validation of pulsed-CEST MRI. In addition, we showed that for diamagnetic CEST agents undergoing slow chemical exchange, the optimized pulsed-CEST MRI contrast is comparable to that of CW-CEST MRI. The simulation has been further validated with both phantom and in vivo applications. In summary, our results showed that pulsed-CEST MRI is feasible with optimized RF irradiation, and remains promising for clinical translation.

Acknowledgments

This study was supported in part by grants from AHA/SDG 0835384N, NIH/NIBIB 1K01EB009771, NIH/NINDS R21NS061119 and NIH/NCRR P41RR14075. This work has been presented at the Gordon Research Conference of in vivo MR, July 2010.

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Fig. 1.

Illustration of CW- and pulsed-CEST MRI sequences, which includes a long RF irradiation module followed by fast image readout. In comparison with the CW-CEST MRI, the pulsed-CEST MRI sequence has multiple variable parameters to optimize including the RF pulse duration and flip angle.

Fig. 2. Evaluation of pulsed-CEST MRI contrast as a function of RF flip angle. a) Four simulated Z-spectra with RF flip angles of being 90° , 180° , 360° and 540° , respectively. We assumed $K_{sw}=50 \text{ s}^{-1}$, $\Delta\omega_s=1.9 \text{ ppm}$ and $\tau=15 \text{ ms}$. b) Simulated pulsed-CEST contrast typically shows large contrast when the flip angle is about 180° – 220° , and bottoms when the flip angle increases beyond 360° . The optimal flip angle is evaluated as a function of exchange rate (Fig. 2c) and chemical shift (Fig. 2d).

Fig. 3.

Evaluation of pulsed-CEST MRI contrast as a function of RF irradiation pulse duration. a) Three simulated Z-spectra with RF duration of 5, 15 and 30 ms. We assumed $K_{sw}=50 \text{ s}^{-1}$, $\Delta\omega_s=1.9 \text{ ppm}$ and $\Phi=180^\circ$. b) Simulated pulsed-CEST MRI typically shows large contrast when the duration is above 10 ms. The optimal RF pulse duration is shown to decrease with exchange rate (Fig. 3c) and chemical shift (Fig. 3d).

Fig. 4.

Comparison of pulsed- and CW-CEST MRI contrast and their optimal experimental conditions. a) Although the optimized pulsed-CEST MRI contrast is approximately equal to that of CW-CEST MRI for slow exchange rates, it decreases when the exchange rate becomes higher. b) The loss of pulsed-CEST contrast from that of CW-CEST contrast increases with exchange rate, consistent with Fig. 4a. c) The optimal RF amplitude for CW-CEST MRI increases with both exchange rate and chemical shift. d) The mean RF amplitude for pulsed-CEST MRI and the optimal RF power for CW-CEST can be described by linear regression, being $B_{1_pulse_opt} = 0.28 \cdot B_{1_cw_opt}^2 + 1.04 \cdot B_{1_cw_opt} + 0.006 \mu T$.

Fig. 5.

Experimental evaluation of pulsed-CEST MRI. a) Illustration of multi-compartment creatine-gel pH phantom. b) pH-weighted CW-CEST MRI of the phantom ($B_1=1.25 \mu T$). c) pH-weighted pulsed-CEST MRI of the phantom ($\phi=257^\circ$ (after RF field calibration) and $\tau=20$ ms). d) Pulsed-CEST MRI contrast as a function of flip angle ($\tau=20$ ms). e) Pulsed-CEST MRI contrast as a function of pulse duration ($\phi=257^\circ$). f) 2-D histogram of optimal flip angle and pulse duration. g) Amine exchange rate is estimated from previously calibrated base-catalyzed chemical exchange relationship and titrated pH. h) Comparison of pulsed-CEST ($\phi=257^\circ$ and $\tau=20$ ms) and CW-CEST ($B_1=1.25 \mu T$) contrast as a function of exchange rate. i) The difference between pulsed- and CW-CEST MRI contrasts increases at higher exchange rate.

Fig. 6. in vivo evaluation of pH-weighted APT MRI. MCAO induced ischemic tissue damage can be observed in ADC map (a), which also displays hypointensity in pH-weighted APT maps acquired with CW-CEST (b, $B_1=0.75 \mu\text{T}$) and pulsed-CEST (c, $\tau=15 \text{ ms}$, $\phi=180^\circ$), with their $\text{CESTR}_{\text{asym}}$ found to be $-6.4 \pm 1.4\%$ (mean $\pm$ S.D.) and $-5.9 \pm 1.2\%$, respectively.