Respiratory triggered Chemical Exchange Saturation Transfer MRI for pH Mapping in the Kidneys at 3T

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Introduction

The development of contrast enhanced MRI to report on local pH values would be of high clinical interest, because several pathologies are associated with pH changes like lowered extracellular pH in tumors [1] or compromised/impaired renal function [2]. There is yet no clinical imaging modality available which enables non-invasive pH measurements. CEST (chemical exchange saturation transfer)-MRI has shown promise, because chemical exchange rates are strongly pH-dependent, and several CEST contrast agents are under investigation to serve as pH reporters [3,4]. One promising candidate is Iopamidol [5], which exhibits two amide proton (NH) pools with different chemical shift (CS), thus allowing a ratiometric pH measure independent from the baseline agent concentration [6]. The purpose of the present study was to extend existing CEST-MRI methodology to anatomical regions strongly affected by physiological motion. As an example, we address CEST-based pH imaging of the kidneys, where compensation of the respiratory motion is essential. The combination of a respiratory trigger with the typical long RF saturation imposed for CEST-MRI is not straightforward, because the time scales of breathing periods and RF saturation pulses are similar. We propose a breathing triggered CEST technique with continuous pulsed RF saturation during the wait time for the trigger event. Feasibility of motion compensated CEST pH mapping in the kidneys of a rat is demonstrated on a clinical MR scanner.

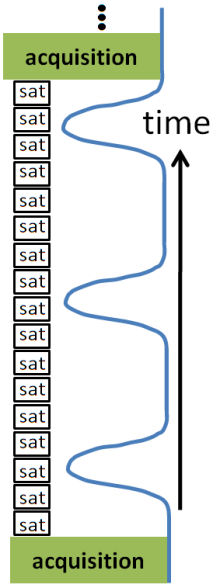

Figure 1: Scheme for a motion triggered CEST sequence. RF saturation is divided into elements ("sat", e.g. 60 ms), after which the motion state is probed. Saturation may be extended over multiple breathing cycles, and acquisition is placed in the desired motion phase.

Methods

The study was performed on a 3.0T clinical scanner (Achieva, Philips Healthcare, NL) using an 8-channel whole-body rat coil (Rapid Biomedical, Germany) for reception and the body-coil for RF transmission. 3 male Sprague-Dawley rats (286±74 g; age 10±4 weeks) were anesthetized with isofluorane and injected with 2.4 ml/kg of Iopamidol (370 mg/ml; Bracco, Italy) according to a protocol approved by the University of Maastricht animal ethics committee. Acquisition software was modified for pulsed RF saturation during the wait time imposed by the breathing trigger, according to Fig.1, and to use the RF amplifier decoupling mode (100% duty-cycle) for arbitrarily long RF pulses [8]. Delay sequence elements (100 ms) were replaced by RF saturation elements, and the motion state was probed after each element. RF saturation could be applied over an arbitrary number of breathing cycles and data acquisition was placed at end-expiratory phases. A dual-echo 2D segmented GRE sequence was used: matrix 344×84, resolution 0.7×0.7×4.0 mm^3, 3 breathing cycles (≈3 sec) per segment, 4 segments per saturation off-resonance, TR=19 ms, TE_1/TE_2=5.4/13.3 ms, α=30°, pixel bandwidth 134 Hz, 19 frequency points in steps of 0.43 ppm around $\Delta\omega$=±4.63 ppm, covering the two NH pools (4.2 ppm/5.5 ppm), and one far off-resonant (S_0, $\Delta\omega$=-160 ppm), saturation pulse elements 62.5 ms (Sinc-Gauss), $B_{1,rms}$=2.4 µT. The acquisition time for one time point was about 6 minutes. Serial measurements were performed pre- and post-injection (23 time points, 110 min). δB_0 maps were calculated by iterative Dixon/IDEAL reconstruction [7,8]. The asymmetric magnetization transfer ratio $MTR_{asym}[\Delta\omega]=(S[-\Delta\omega]-S[+\Delta\omega])/S_0$ was calculated based on δB_0 corrected, point-wise interpolated images S[-Δω] and S[+Δω] from the sum of both echoes. A ratiometric value R of the two NH pools was obtained by

$$R=\frac{(1-MTR_{asym}[4.2\,ppm])\,MTR_{asym}[5.5\,ppm]}{(1-MTR_{asym}[5.5\,ppm])\,MTR_{asym}[4.2\,ppm]}$$

[6] and calibrated for pH[R] by a phantom experiment with identical parameters and 5 vials with Iopamidol (60mM) at different pH.

Results and Discussion

The respiratory triggered CEST sequence resulted in motion artifact-free images (Fig.2a, selected saturation off-resonance) and MTR_{asym} maps of the rat kidneys (b/c). As all waiting time for trigger is used for the pulsed RF saturation, scan time efficiency was maintained as compared to a standard, non-triggered CEST acquisition. Operating near full saturation ensures that the CEST contrast does not vary significantly with typical changes in the breathing rate. The δB_0 corrected maps of MTR_{asym} at 4.2 ppm (b) and 5.5 ppm (c) from a selected time point 95 min post-injection clearly show a strong CEST effect in the renal pelvis of both kidneys. A pH map obtained by ratiometric analysis and calibration of all time points (d) shows a uniform pH of about 6.5 in the pelvis, but only scattered results from the medulla, where the CEST contrast was low. In the pelvic area, a pH time course could be measured (e). Monitoring of the pH distribution, time evolution and potential impairment between the two kidneys may provide important physiological information. The technique can be extended to human applications in the future, because Iopamidol is approved for human use as CT contrast agent which simplifies the approval for MR. An important pre-requisite is the combination of a breathing trigger with long RF saturation as explored in this work.

Conclusion

A robust and efficient motion-triggered CEST sequence was implemented and successfully tested *in vivo* in the context of non-invasive pH mapping.

Acknowledgement

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References:[1] *Gillies RJ et al., IEEE Eng Med Biol Mag 23:57 (2004)* [2] *Periera PC et al., Curr Genomics 10:59 (2009)* [3] *Aime S et al., MRM 47:639 (2002)* [4] Pikkemaat *JA et al., Contrast Med Mol Imaging 2:229-239 (2007)* [5] *Aime S et al., MRM 53:830-834 (2005)* [6] *Longo DL et al., MRM 2010 Oct 14 [Epub]* [7] *Reeder SB et al., MRM 51:35 (2004)* [8] *Keupp J et al., Proc. ISMRM 18:338 (2010)*

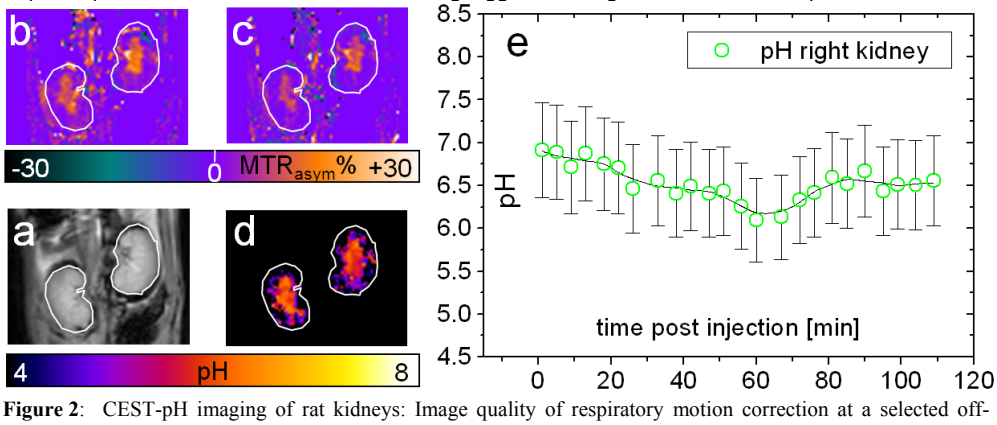

Figure 2: CEST-pH imaging of rat kidneys: Image quality of respiratory motion correction at a selected off-resonance saturation (a) is a good basis for the CEST mapping at 4.2 ppm (b) / 5.5 ppm (c). Ratiometric evaluation and pH calibration allows to measure pH in both kidneys as average over all post-injection time points (d) and to monitor the time course of pH the kidney pelvis (e).