Non-invasive CEST-MRI Measurement of pH in the Human Kidneys using an Approved CT Contrast Agent

J. Keupp[1], I. Dimitrov[2,3], S. Langereis[4], O. Togao[3], M. Takahashi[3], and A. D. Sherry[3]
[1]Philips Research Europe, Hamburg, Germany, [2]Philips Healthcare, United States, [3]Advanced Imaging Research Center, UT Southwestern Medical Center, Dallas, Texas, United States, [4]Philips Research Europe, Eindhoven, Netherlands

Introduction

The development of MR contrast agents to report on tissue pH 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]. CEST (chemical exchange saturation transfer)-MRI is particularly promising for pH mapping as the proton site exchange is highly pH-dependent. Several research groups have developed exogenous contrast agents targeting pH mapping in the physiological region [3,4]. While some of these agents are highly sensitive to pH changes, they may have an associated *in vivo* toxicity, which will need to be further investigated. Fortuitously, a clinically approved CT agent, Iopamidol, has been shown to have exchangeable protons that generate CEST contrast [5]. It provides two amide proton (NH) pools with different chemical shift (CS), thus allowing a ratiometric pH measure independent from the local agent concentration, as recently demonstrated in a pre-clinical study [6]. The purpose of the present study was to determine, if Iopamidol can be used for *in vivo* human pH measurement in the renal pelvis using respiratory triggered CEST-MRI on a clinical 3T scanner.

Methods

All experiments were performed on a clinical 3T scanner (Achieva, Philips Healthcare, NL) with body coil RF transmission and a 6-channel bi-planar torso coil for reception. Acquisition software was modified to use the low-power mode (RF amplifier decoupling mode, 500 W, 100% duty-cycle) for long pulsed saturation and to apply the RF saturation pulses during the wait time for breathing trigger. A maximum number of saturation pulses was pre-defined and checked during runtime to enable SAR-safe operation. Three healthy volunteers were scanned using an IRB-approved protocol for *i.v.* bolus-injection of 100 ml of Iopamidol (Isovue-300®, Bracco, Italy) at a rate of 2ml/s. All subjects were well hydrated and creatinine levels were assessed prior to the experiment. CEST imaging was initiated during the injection procedure and continued for 60 minutes afterwards. A dual-echo 2D segmented GRE sequence was used: FOV (400 mm)^2, coronal orientation, matrix 228×226, resolution 1.75×1.77×6 mm^3 (reconstruction 1.67 mm), one segment per breathing cycle (average interval 4.3 sec), 4 segments per off-resonance frequency, TR=9.3 ms, TE_1/TE_2=2.7/6.1 ms, SENSE acceleration factor 2, α=30°, pixel bandwidth 330 Hz, 19 saturation frequency points in steps of 0.43 ppm around $\Delta\omega$=±4.64 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), $B_{1,sat\text{-}rms}$=1.5 µT and about 6 minutes scanning time (depending on actual breathing intervals). δB_0 maps were calculated by iterative Dixon/IDEAL reconstruction [7,8]. In addition, standard 2D B0 maps (two echoes, ΔTE=1ms) were recorded. Maps of the asymmetric magnetization transfer ratio $MTR_{asym}=(S[-\Delta\omega]-S[+\Delta\omega])/S_0$ were calculated based on δB_0 corrected, point-by-point interpolated images S[-Δω] and S[+Δω]. A ratiometric value R of the two NH pools was obtained by [6]

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

and calibrated for pH(R) via a phantom experiment using identical image parameters and 5 vials prepared with Iopmidol (60 mM) at different pH values (buffer).

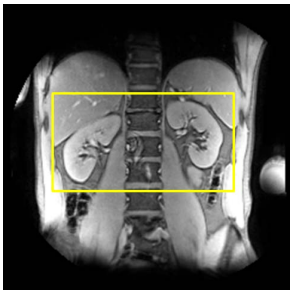

Fig 1. A representative single-offset saturation image showing good motion correction in the abdomen (yellow box: ROI).

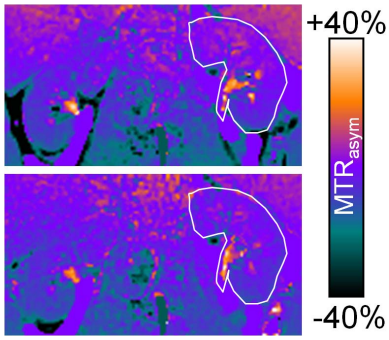

Fig 2. CEST maps at 4.2ppm (top) and 5.5 ppm (bottom) acquired 11 minutes after Isovue injection. Clear enhancement is seen in the left and right renal pelvis.

Results and Discussion

The volunteer experiments were successfully completed, and the triggered CEST technique provided a stable breathing motion compensation with good image quality as visible in Fig. 1. A significant CEST effect was observed from a few minutes post-injection on both NH pools, predominantly in left/right renal pelvis (Fig. 2). At about 20 minutes, a maximum MTR_{asym}[4.2ppm]=(27±3)% was observed in the right pelvis. The full time course is shown in Figure 3 for both NH pools. From this data, a time course of pH values could be calculated (Fig.4). In the left pelvis, the CEST effect was near to noise level after about 25 minutes, such that the ratiometric pH could not be evaluated beyond this time point. As the visible CEST effect is mostly confined to the pelvis, only regional evaluation of the pH was feasible. Nevertheless, absolute pH values from both kidneys could provide important clinical information on kidney function and potential impairment. To our knowledge, this is the first reported application of exogenous CEST agents for non-invasive pH mapping in humans.

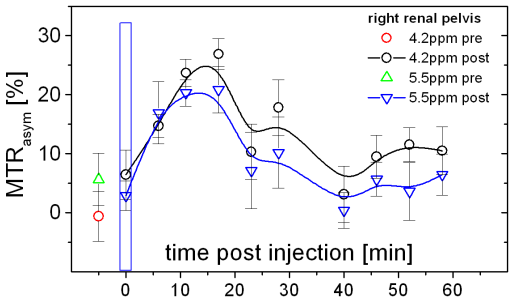

Fig 3. Time evolution of the CEST contrast in the right kidney. CEST effects up to 25% are recorded

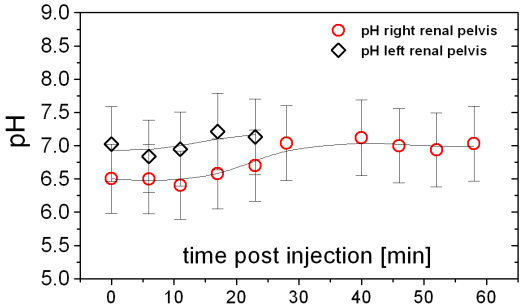

Fig 4. Time evolution of the pH measurements in the left and right kidney pelvis.

References

[1] *Gillies RJ et al., IEEE Eng Med Biol Mag 23:57 (2004)* [2] *Periera PC et al., Curr Genomics 10:51 (2009)* [3] *Aime S et al., MRM 47:639 (2002)* [4] *Pikkemaat JA et al., Contrast Med Mol Imaging 2:229 (2007)* [5] *Aime S et al., MRM 53:830 (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)*