Chlorine (^{35}Cl) Magnetic Resonance Imaging of the Human Brain and Muscle

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Introduction

Chlorine (Cl^-) is the most important anion in the human body and is involved in many physiological processes. It plays a crucial role in controlling the ionic composition of the cytoplasm and the volume of cells [1]. In skeletal muscle, Cl^- exhibits a passive distribution in response to the resting membrane potential. This results from the very high Cl^- conductance, making up ~80% of the total membrane conductance at rest [2]. Thus, the resting potential of muscle cells can be calculated from the intra- and extracellular Cl^- concentration. Contrary to sodium (^{23}Na) magnetic resonance imaging (MRI), which is more frequently used in clinical research, to date ^{35}Cl-MRI has only been applied for small animal imaging [3]. In this work, we implemented ^{35}Cl-MRI and evaluated its feasibility for high field (7 T) imaging.

Methods

^{35}Cl-MRI was conducted on a 7 T whole body MR system (Magnetom 7 T, Siemens Healthcare, Erlangen, Germany) using a double-resonant (^{35}Cl/ ^{1}H), quadrature birdcage coil (inner coil diameter: 22 cm) (QED, Mayfield Village, Ohio, USA). The monitoring of the specific absorption rate (SAR) on the ^{35}Cl frequency (29.15 MHz) was implemented by Siemens Healthcare (Erlangen, Germany). To compare relaxation times, ^{23}Na-MRI was performed using a double resonant quadrature birdcage coil (Rapid Biomed GmbH, Rimpar, Germany).

Phantom-study (c.f. Fig. 1): Sodium chloride (NaCl) solutions (153.9 mmol/l) containing different agar gel concentrations (0%, 1%, 2%, 3%, 4%) were examined to compare ^{23}Na and ^{35}Cl-relaxation times. For pure NaCl solution, mono-exponential fitting was applied to fit 3D density-adapted projection reconstruction (DA-3DPR) [4] multi-echo data (TE = 0.3/ 1/ 2/ …/ 55 ms; TR(^{23}Na/^{35}Cl) = 300/200 ms; $\alpha = 90°$; readout length $T_{RO} = 5$ ms; 8 echos each; 8000 projections; nominal spatial resolution: (5 mm)^3). To calculate T_2^* of the agar gel phantoms, a bi-exponential model with a short (T_{2s}^*; 60%) and a long relaxation component (T_{2l}^*; 40%) was applied. Inversion recovery imaging using different inversion times (starting from TI = 1 ms to TI(^{23}Na/^{35}Cl) = 300/150 ms) and mono-exponential fitting were used to determine T_1 relaxation times (TE = 0.3 ms, TR(^{23}Na/^{35}Cl) = 500/300 ms; $T_{RO} = 5$ ms; 6000 projections; (6 mm)^3).

Brain-imaging (c.f. Fig. 2): **(1)** To estimate relaxation times in the human brain, one subject was examined with 7 multi-echo sequences (TE = 0.55/ 0.75 1/ 2/ …/ 13 ms; TR = 35 ms; $\alpha = 60°$; $T_{RO} = 5$ ms; (8.9 mm)^3; 8 echoes each; 6000 projections; $T_A = 3$ min 30 s). Additionally, another subject was examined using 10 inversion recovery sequences (TE/ TR = 0.8/ 150 ms, TI = 3/ 6/ 9/ 12/ 15/ 20/ 25/ 30/ 40/ 50 ms, $T_{RO} = 5$ ms, (10 mm)^3; $T_A = 7$ min 30 s).
(2) 3D density-adapted projection reconstruction images of the human brain were acquired with minimized relaxation weighting (TE/ TR = 0.6/ 90 ms; $\alpha = 90°$; $T_{RO} = 10$ ms; pulse length: 1.1 ms; 9000 projections; (6 mm)^3; Hamming filtering; $T_A = 13.5$ min). To suppress liquids, an inversion recovery (IR) preparation was applied (TE/ TR = 0.8/ 150 ms; TI = 24 ms; $T_{RO} = 5$ ms; 4000 projections; (9 mm)^3; Hamming filtering; $T_A = 10$ min).

Muscle-imaging (c.f. Fig. 3)*:* **(1)** Images with 12 different echo times (TE = 0.35/ 0.55/ 0.75/ 1/ 1.25/ 1.5/ 1.75/ 2/ 2.5/ 3/ 3.5/ 4 ms; TR = 35 ms; 6000 projections; (11 mm)^3; Hamming filtering; $T_A = 3$ min 30 s) were used to calculate T_2^* relaxation times of four healthy subjects (Tab. 1).
(2) The average Cl^- concentration was estimated in soleus and gastrocnemius muscle using the fitted signal intensity (TE = 0 ms) and the signal of the reference tube 2 (TE = 0.35 ms image).

Results

^{35}Cl images of the human brain with SNRs of 15 (brain parenchyma) and 45 (CSF) could be acquired with an isotropic voxel size of (6 mm)^3 in 13.5 min (Fig. 2a). ^{35}Cl exhibits much shorter relaxation times than ^{23}Na (Fig. 1), in brain parenchyma ^{35}Cl-relaxation times of $T_{2s}^* = 1.1(1)$ ms, $T_{2l}^* = 6.2(3)$ ms and $T_1 = 10.5$ ms were measured. The differences in T_1 relaxation times of ^{35}Cl could be used to selectively suppress signal from ^{35}Cl ions in cerebrospinal fluid (Fig. 2b). In skeletal muscle, the calculated Cl^- concentrations and relaxation times showed a strong inter-individual variation of more than a factor of 2 (Tab. 1) - in general - higher Cl^- concentrations were found in older subjects (Fig. 3).

Discussion and Conclusion

In this work ^{35}Cl images were acquired for the first time in humans. ^{35}Cl-MRI of the brain and muscle is possible within clinically feasible measurement times (< 15 min) and spatial resolutions of (6 mm)^3 (brain) and (11 mm)^3 (muscle). Strong inter-individual variations of the measured Cl^- concentrations in skeletal muscle (c.f. Fig. 3) might be caused by differences in concentrations, residual T_2^* weighting, or partial invisibility of the ^{35}Cl-signal. In future, ^{35}Cl-MRI should complement ^{23}Na-MRI and enable a better analysis of (patho-) physiological cellular processes.

References

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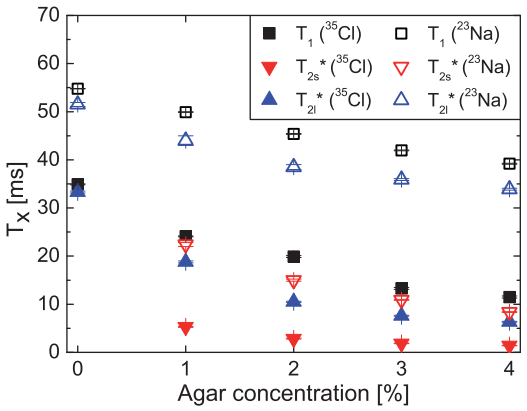

Fig. 1: T_1 and T_2^* ^{23}Na and ^{35}Cl relaxation times of 153.9 mmol/l sodium chloride solution containing different concentrations of agar gel. ^{35}Cl exhibites much shorter relaxation times than ^{23}Na.

Tab. 1: ^{35}Cl T_2^*-relaxation times and estimated chloride concentrations of human calf muscle. Error bars from the linear regression are given in parentheses.

Subject (age, sex)	Concentration [mmol/l]	T_{2s}^* [ms]	T_{2l}^* [ms]
#1 (24y, f)	11 (2)	0.3 (2)	2.5 (7)
#2 (27y, m)	8 (2)	0.5 (3)	2.7 (6)
#3 (66y, m)	19 (2)	0.8 (3)	3.0 (2)
#4 (71y, m)	18 (1)	0.64 (7)	4.1 (3)

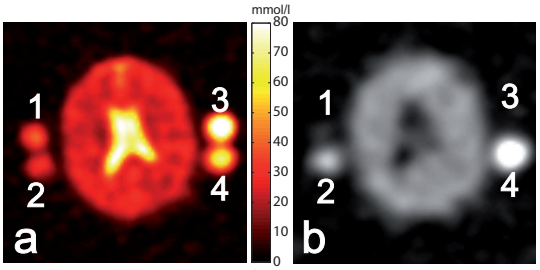

Fig. 2: Exemplary slices of ^{35}Cl-datasets of the human brain. Reference tubes containing NaCl solution (1, 2: 51.3 mmol/l; 3,4: 102.6 mmol/l) and 4% agar gel (2, 4) were used. a) ^{35}Cl-concentration map. b) ^{35}Cl-signal from pure NaCl solution (1, 3) and CSF can be well suppressed.

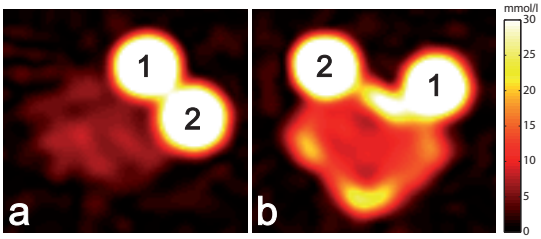

Fig. 3: Exemplary slices of ^{35}Cl-datasets of the human calf muscle. Reference tubes with 51.3 mmol/l NaCl and 0% (tube 1) and 4% agar (tube 2) were used. a) Subject #1 (24y, f). SNR: 15. b) Subject #2 (71y, m). SNR: 7.

Acknowledgement:
Parts of this work were supported by the Eva Luise and Horst Köhler Foundation and the German Federal Ministry of Education and Research (project DOT-MOBI; 01IB08002).