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 7T, Siemens Healthcare, Erlangen, Germany) using a double-resonant ($^{35}$Cl/¹H), 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/ 0.75/ 1/ 2/ …/ 15 ms; TR = 35 ms; α = 90°, readout length $T_{RO} = 5$ ms; 8 echoes each; 8000 projections; nominal spatial resolution: (5 mm)⁵). To calculate $T_1$ of the agar gel phantoms, a bi-exponential model with a short ($T_2^*$; 60%) and a long relaxation component ($T_2^*$; 40%) was applied. Inversion recovery imaging was acquired using different inversion times (starting from T₁ = 1 ms to T₁ = 6.2/150 ms) and mono-exponential fitting was used to determine $T_1$ relaxation times (TE = 0.3 ms, TR($^{35}$Na/Cl) = 500/300 ms; $T_{RO} = 5$ ms; 6000 projections; (6 mm)).

- **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/ …/ 10/ 12 ms; TR = 35 ms; α = 60°; $T_{RO} = 5$ ms; (8.9 mm)³, 8 echoes each; 6000 projections; $T_2 = 3$ min 30 s). Additionally, another subject was examined using 10 inversion recovery sequences (TE/ TR = 0.8/ 150 ms; T₁ = 3/ 6/ 9/ 12/ 15/ 20/ 25/ 30/ 40/ 50 ms; $T_{RO} = 5$ ms; (10 mm); $T_2 = 7$ min 30 s). (2) Using multi-echo sequences, images of the human brain were acquired with minimized relaxation weighting (TE/ TR = 0.6/ 90 ms; α = 90°; $T_{RO} = 10$ ms; pulse length: 1.1 ms; 9000 projections; (6 mm); Hamming filtering; $T_2 = 13.5$ min). To suppress liquids, an inversion recovery (IR) preparation was applied (TE/ TR = 0.8/ 150 ms; T₁ = 24 ms; $T_{RO} = 5$ ms; 4000 projections; (9 mm); Hamming filtering; $T_2 = 10$ min).

- **Muscle-imaging (c.f. Fig. 3):** (1) Images with 12 different echo times (TE/ TR = 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); Hamming filtering; $T_2 = 3$ min 30 s) were used to calculate $T_2^*$ relaxation times of four healthy subjects (Tab. 1).

- **Brain-imaging (c.f. Fig. 2):** (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 $T_2^*$ = 1.1(1) ms, $T_2^*$ = 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 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 exhibits 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.

<table>
<thead>
<tr>
<th>Subject (age, sex)</th>
<th>Concentration [mmol/l]</th>
<th>$T_2^*$ [ms]</th>
<th>$T_2^*$ [ms]</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 (24y, f)</td>
<td>11 (2)</td>
<td>0.3 (2)</td>
<td>2.5 (7)</td>
</tr>
<tr>
<td>#2 (27y, m)</td>
<td>8 (2)</td>
<td>0.5 (3)</td>
<td>2.7 (6)</td>
</tr>
<tr>
<td>#3 (66y, m)</td>
<td>19 (2)</td>
<td>0.8 (3)</td>
<td>3.0 (2)</td>
</tr>
<tr>
<td>#4 (71y, m)</td>
<td>18 (1)</td>
<td>0.64 (7)</td>
<td>4.1 (3)</td>
</tr>
</tbody>
</table>

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 gel (tube 2) were used. a) Subject #1 (24y, f). SNR: 15. b) Subject #2 (71y, m). SNR: 7.