Chlorine ($^{35}\text{Cl}$) MRI in Humans: CT Alterations do not Correspond to Disease-Related Na$^+$ Changes

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Target Audience: Scientists and physicians interested in the field of non-proton MRI

Purpose: Chlorine (Cl) is the most abundant anion in the human body and is involved in many physiological processes. Cl channels of the cell membrane contribute to volume regulation, ionic homeostasis, transepithelial transport and regulation of electrical excitability [1]. Skeletal muscle exhibits a very high Cl conductance [2]. Thus, the resting potential of muscle cells can be estimated from the intra- and extracellular Cl concentration. Studies with human muscle cells indicate that their proliferation is linked to the membrane potential [3]. Cl channels also play a crucial role in glial cell migration and invasion [4]. Therefore, the non-invasive measurement of the cellular Cl concentration and distribution is highly desirable and might provide insights into pathophysiological processes of several diseases.

$^{35}\text{Cl}$ MRI has been applied for small animal imaging [5] and recently we demonstrated its feasibility for imaging of the healthy human muscle and brain [6]. In this work we present first results for the visualization of pathophysiological processes in humans.

Methods: $^{35}\text{Cl}$ MRI was conducted on a 7-T whole-body MR system (MAGNETOM T7, Siemens AG, Healthcare Sector, Erlangen, Germany) using a dual tuned ($^1\text{H}$/$^{35}\text{Cl}$), quadrature birdcage coil (inner coil diameter: 22 cm) (QED, Mayfield Village, Ohio, USA).

To evaluate if $^{35}\text{Cl}$ MRI can yield additional information to established techniques, $^{23}\text{Na}$ MRI was performed using a dual tuned ($^1\text{H}$/$^{23}\text{Na}$) quadrature birdcage coil (Rapid Biomed GmbH, Rimpar, Germany). All $^{23}\text{Na}$ and $^{35}\text{Cl}$ MRI sequences were based upon a density-adapted 3D radial projection reconstruction pulse sequence [7]. Signal intensities were normalized to reference tubes containing saline solution and agar gel. Additionally to the 7 Tesla MR data, $^{35}\text{Cl}$ MRI data acquired at a 3 Tesla were available. To evaluate the feasibility of $^{35}\text{Cl}$ MRI to visualize pathophysiological processes, results from one patient with a confirmed glioblastoma, one enchondroma of the left distal femur and from one patient with a muscular ion channel disease (hypokalemic periodic paralysis) are presented.

Parameters Glioblastoma Patient (c.f. Fig. 1): To assess the local Cl concentration, relaxation weighting was minimized using a short echo time (TE = 0.7 ms) and a long repetition time (TR = 65 ms) ($^{35}\text{Cl}$ conc.). Additional parameters: readout duration: $T_{RO} = 10$ ms; $\alpha = 90^\circ$; nominal resolution: $\Delta x = (6 \text{ mm})$; Hamming filtering; acquisition time $T_{acq} = 95 \text{ min}$. To suppress signal from Cl with longitudinal relaxation times like cerebrospinal fluid, an inversion recovery (IR) sequence was applied ($^{35}\text{Cl}$ IR). Parameters: $TE = 0.8$ ms; $TR = 150$ ms; $T_1 = 24$ ms; $\Delta x = (10 \text{ mm})$; $T_{RO} = 5$ ms; $T_{acq} = 10$ min. $^{23}\text{Na}$ MRI sequences with similar contrasts were applied. Parameters: $^{23}\text{Na}$ conc.; TE/ TR: $T_E = 0.35/ 120$ ms; $T_{RO} = 10$ ms; $\alpha = 90^\circ$; $\Delta x = (3 \text{ mm})$; Hamming filtering; $T_{acq} = 10$ min; $^{23}\text{Na}$ IR: TE = 0.75/ 185 ms; $T_{RO} = 10$ ms; $\Delta x = (4.5 \text{ mm})$; $T_{acq} = 9$ min 52 s.

Parameters Enchondroma Patient (c.f. Fig. 2): $^{35}\text{Cl}$ MRI: TE/ TR = 0.35/ 60 ms; $T_{RO} = 5$ ms; $\alpha = 90^\circ$; $\Delta x = (6 \text{ mm})$; 3 averages; $T_{acq} = 30$ min. $^{23}\text{Na}$ MRI: TE/ TR = 0.4/ 101 ms; $T_{RO} = 10$ ms; $\alpha = 90^\circ$; $\Delta x = (6 \text{ mm})$; 3 averages; $T_{acq} = 30$ min 18 s. $^{35}\text{Cl}$ MRI: TE$_{0} = 0.35$, 0.55, 0.75, 1.00, 1.25, 1.50, 2.75 ms; $T_E = 4$, 4.6, 5.2, 6.0, 6.6, 7.3, 8; $TE = 8$, 9, 10, 11, 12, 13, 14 ms; $\alpha = 90^\circ$; multi-echo sequences (5 min each); TR = 60 ms; $T_{acq} = 2.5$ ms; $\Delta x = (11 \text{ mm})$; $^{23}\text{Na}$ MRI: TE = 0.35 ms; TR = 160 ms (93 ms); $T_{acq} = 10$ ms; $\alpha = 90^\circ$ (45$^\circ$); $\Delta x = (4 \text{ mm})$. Corrections for $B_0$ and $B_1$ inhomogeneities were performed.

Results: Concentration weighted imaging revealed increased $^{23}\text{Na}$ and $^{35}\text{Cl}$ signal intensities in enhancing and non-enhancing parts of the glioblastoma (Fig. 1). In IR imaging $^{23}\text{Na}$ and $^{35}\text{Cl}$ MRI showed opposed behavior (Fig. 1). Whereas large parts of the affected area exhibit increased $^{35}\text{Cl}$ IR signal, the $^{23}\text{Na}$ IR signal shows a distinct increase (Fig. 1). In $^{35}\text{Cl}$ and $^{23}\text{Na}$ MRI data of an enchondroma of the left distal femur are shown in figure 2. The measured chloride concentration is approximately 7-fold lower than the sodium concentration. In muscle tissue of the patient with hypokalemic periodic paralysis, the measured Cl concentration is 1.5-fold smaller than the Na$^+$ concentration (Fig. 3).

Discussion and Conclusion: In this work $^{35}\text{Cl}$ images of different pathologies were acquired for the first time in humans. These preliminary results show different signal behavior for $^{23}\text{Na}$ and $^{35}\text{Cl}$ MRI, which demonstrates the fact that Cl does not only act as counterion for Na$^+$. Thus, $^{35}\text{Cl}$ MRI can complement $^{23}\text{Na}$ MRI in clinical research and might enable a better analysis of (patho-)physiological processes in the future.