^{23}Na-MRI contrasts for application in muscular sodium channel diseases

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Introduction

Sodium (^{23}Na) MRI has the potential to noninvasively detect sodium content changes *in vivo* [1]. In previous ^{23}Na-MRI studies of pathological changes either the total tissue ^{23}Na concentration (TSC) was measured [2], or a T_1 weighted approach was used to increase the SNR [3]. Furthermore, it has been demonstrated that in the healthy human brain ^{23}Na fluid signal (e.g. liquor) can be suppressed with an inversion recovery sequence [4]. In this study, these three ^{23}Na-MRI contrasts were applied and compared with regard to the information they provide about the compartments from which the ^{23}Na signal originates. In particular, it was evaluated if the used techniques are capable of providing a strong weighting of the intracellular ^{23}Na. Therefore, the model disease hypokalemic periodic paralysis (HypoPP), a muscular ^{23}Na channelopathy, was selected. In HypoPP, cooling causes an increased open probability of the mutant sodium channels resulting in intracellular ^{23}Na accumulation and muscle weakness [5].

Methods

Two patients with confirmed HypoPP and two healthy volunteers were examined on a 3.0 T clinical MR system (Magnetom Tim Trio, Siemens Medical Solutions, Erlangen, Germany). Images were acquired using a double-resonant (32.59 MHz/ 123.2 MHz) birdcage coil (Rapid Biomed GmbH, Würzburg, Germany).

Three different sodium MRI techniques based on a 3D density adapted projection reconstruction sequence [6] were used.

First, T_1 weighted ^{23}Na images were acquired with the following parameters: TE/TR = 0.3/6 ms; α = 40°; voxel size: 5x5x5 mm^3; 14000 projections; 4 averages; 5 min 36 s.

An Inversion Recovery (IR) sequence was used to suppress sodium signal emanating from ^{23}Na ions in unrestricted environments (e.g. pure sodium chloride (NaCl) solution). Parameters: TE/TR = 0.3/124 ms; TI = 34 ms; voxel size: 6x6x6 mm^3; 5000 projections; 10 min 20 s.

Furthermore, the TSC was measured, providing a basis to compare the ^{23}Na-T1 and ^{23}Na-IR sequences. Parameters: TE/TR = 0.2/100 ms; α = 90°; 5000 projections; voxel size: 5x5x5 mm^3; 8 min 20 s. For the ^{23}Na-T1 and the ^{23}Na-IR sequence an 'apparent' concentration was calculated, using a reference tube (2) containing 0.3% NaCl and 5% agarose gel. Additionally, ^{1}H-imaging with a T2-TIRM sequence was performed. In between the first and second measurement one lower leg was cooled for 25 min, followed by a short exercise (≈ 2 min), provoking an intracellular ^{23}Na-accumulation in the patients' cooled leg. Prior to each measurement the muscle strength was measured according to a grading system proposed by the British Medical Research Council. Taking the concentration weighted images, ROI's (musculus soleus) were selected in 15 slices. In the ^{23}Na-T1 und ^{23}Na-IR images ROI's were selected automatically at the same position, to prevent a biased selection.

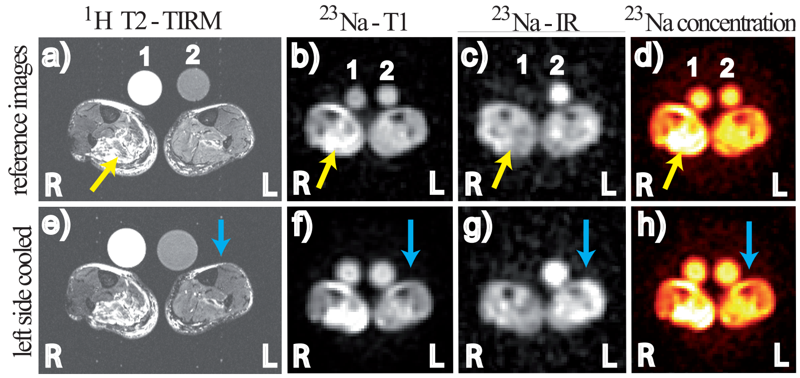

Fig. 1. Images from patient #1 with HypoPP. The reference tubes are labeled by numbers (1: 0.3% NaCl solution; 2: 0.3% NaCl and 5% agarose gel). Edemata in m. soleus and m. gastrocnemius are marked by yellow arrows. In the lower row, the left lower leg (marked by blue arrows) was cooled before the measurement.

Tab. 1. Muscle strength in patients (pat.) with HypoPP and volunteers (vol.). The strength was scored according to the grading system proposed by the British Medical Research Council. (0 = complete paralysis, 5 = full strength)

	pat. #1		pat. #2		vol. #1		vol. #2	
Measurement	ref.	co.	ref.	co.	ref.	co.	ref.	co.
1 (reference)	5	4	5	5	5	5	5	5
2 (one leg cooled)	5	3.5	5	3.5	5	5	5	5

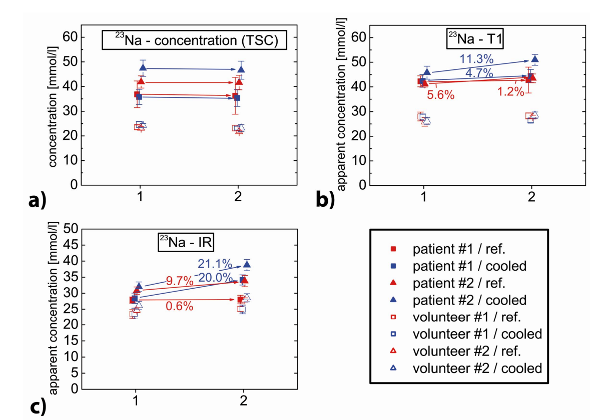

Fig. 2. ROI analysis of the musculus soleus. **1:** reference measurement; **2:** one lower leg was cooled. Red/ blue symbols were used for the non-cooled/ cooled leg. For the ^{23}Na – IR and the ^{23}Na-T1 sequence an 'apparent' concentration was calculated with the reference tube containing 5% agarose gel.

Results

Edemata, which are also visible in the ^{1}H T2-TIRM images (Fig. 1a, e), lead to an elevated sodium concentration (Fig. 1d, h) and to hyper-intensity in the ^{23}Na-T1 (Fig. 1b, f) images. With the ^{23}Na-IR sequence, edemata and the reference tube containing NaCl-solution (1) are suppressed (Fig. 1c, g). The patients showed significantly higher (apparent) sodium concentrations compared to the volunteers (Fig 2), with less distinct differences for the ^{23}Na-IR images (Fig. 2c), since edemata are suppressed. The cooled leg of the patients showed decreased muscle strength; no changes concerning the strength were observed for the volunteers (Tab. 1). The total sodium concentration remained constant after provocation (Fig. 2a), whereas the T_1 weighted measurements showed slightly increased signal intensity (Fig. 2b). The most pronounced increases after cooling were observed in the ^{23}Na-IR images (Fig. 1c, g; Fig. 2c). The volunteers showed no significant changes after cooling in all measurements.

Discussion and Conclusion

This study demonstrates that the ^{23}Na-IR sequence is well suitable to highlight an intracellular sodium accumulation caused by provocation of the lower leg muscles in HypoPP. The increase in signal intensity can be attributed to shorter T_1 relaxation times in the intracellular space compared to extracellular sodium compartments. This is also well in accordance with the tendency of an increased signal intensity in the ^{23}Na-T1 images and unchanged total sodium concentrations. The less pronounced signal increase for the ^{23}Na-T1 sequence when compared to the ^{23}Na-IR sequence can by explained with the fact that the latter provides stronger T_1-weighting. Furthermore, the ^{23}Na-IR sequence suppresses background signal of muscular edemata that affects the interpretation of conventional sodium images. It was shown that with the ^{23}Na-IR sequence a strong weighting of the intracellular space can be obtained and together with a concentration weighted approach, valuable information as to from which compartments the sodium signal originates can be provided.

References

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