MRI assessment of changes in calf fluid level during medication challenge

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Introduction

Fluid retention is one of the most common side effects associated with long term use of many medications ([1-4]). While the clinical assessments of marked edema are straight forward, early detection of modest fluid retention is limited by the insensitivity of these measures. MRI has been exploited to assess the efficacy of medications to increase tissue perfusion in heart and other organs ([5]). However, to our knowledge, there are no reports in the literature on use of MRI to detect iatrogenic fluid retention. The purpose of this study is to investigate the feasibility of using MRI to detect early fluid retention in healthy subjects receiving medication challenge. Both proton (^{1}H) and sodium (^{23}Na) MRI were used in this study for their differential sensitivities to fluid and sodium distributions between intra and extra cellular compartments. Fludrocortisone and nifedipine, known to increase body fluid, were administered in this study. In addition, standard clinical parameters such as body weight, calf circumference and volume, and assessment of pitting were also measured for comparison. Our data indicate that ^{23}Na MRI can detect changes in body fluid level associated with administration of nifedipine and fludrocortisone at early stages.

Methods & Materials

Subjects: Eleven healthy, young male subjects (age: 26±6, body weight 170±18 lbs) were recruited under a protocol approved by local IRB. They were randomly divided into two groups: five received nifedipine (3 weeks) and six were administered fludrocortisone (2 weeks). Each subjects received a weekly MR visit that included both ^{1}H and ^{23}Na scans.

The subjects were asked to comply with a low sodium diet (<3000mg per day) for 48 hours prior to the MRI visits. Before going into the MRI scanner, they were requested to sit still for one hour with their feet resting gently on the floor. The mid calf of each subject was marked during the whole study for consistency of image location and measurement of calf circumference. The volume of the calf was measured using a volume displacement apparatus ([6]).

MRI The ^{23}Na MRI was conducted on a 4T scanner (INOVA, Varian Inc, CA) with a quadratural phased array and ^{1}H MRI was conducted on a 3T scanner (Trio, Siemens AG, Germany) using a CP volume coil. Axial images of both legs were acquired at mid calf repeatedly for ~90 minutes at a temporal resolution of 3 minutes/time point for ^{1}H and 5.7 minutes/time point for ^{23}Na ([7]). The ^{23}Na images were acquired with a 3D gradient echo sequence at TR/TE = 20/2.5, α=45˚, matrix = 16x64x128, slab thickness 192 mm, FOV = 280x280, TA = 5.5 minutes. The ^{1}H images were acquired with a spin-echo sequence at TE/TI/TR = 15/180/800, FOV = 170x270mm, slice thickness 8 mm, matrix 160x256, TA = 2.42 minutes.

Data analysis ROI was placed within the muscle regions across the time series by an operator blinded to the outcome of the measurement. The changes in MR signals and the clinical parameters are presented as mean ± standard error over the treatment groups for each visit for comparison between baseline and challenge as well as follow-up.

Results

Following postural change, ^{1}H (-7%) and ^{23}Na (-11%) signal intensities showed a general decline over the 90-minutes scan. This decline was consistent with a reduction of fluid level in the imaged volume after the postural change ([7]). Subtraction of the MR images or changes in T2* maps during the scan period indicate that the changes of the ^{1}H and ^{23}Na signals mainly came from gastrocnemius and soleus muscles. During the medication challenges, both groups demonstrated augmented signal declines and a return toward baseline values a week after the medication was stopped. With the mean of the first and second visits as the baseline, the fludrocortisone group showed a larger decline (4%) compared to the nifedipine group (2.5%) (Figures **a** & **b**), suggesting more fluid accumulated in the calf prior to the postural change compared to the baseline.

The fludrocortisone group showed a +1.4% weight gain versus a +0.8% weight increase of those treated with nifedipine during the challenges (Figure **c**). The weight increase started during the first week on the medications, similar to the MRI change. Assessment of pitting indicated no change for those treated with fludrocortisone versus a mild increase for those treated with nifedipine (Figure **d**). Measurements of circumference and volume of the calf showed no consistent change during the medication treatments.

Discussion

The MR signal reduction during the 90-minute scan reflects the amount of fluid shifted out of the imaged volume ([7]). The change of ^{23}Na MRI-signal reduction after the start of fludrocortisone treatment is consistent with an increase in calf fluid during the medication challenge. This increase in fluid level was supported by return to the baseline value during the follow-up visit and consistency with the changes in body weight. Our MRI results suggest that more fluid accumulated during fludrocortisone treatment compared to nifedipine. Fludrocortisone, as a mineralocorticoid, acts on the kidney so as to conserve sodium and excrete potassium. This means that it may have predictable side effects including: excessive thirst and urine production as well as weight gain and excessive apetite, among other symptoms. Nifedipine is known to increase vascular permeability in peripheral vasculature and edema shortly after local injection ([2, 6]) as well as fluid retention that may result from systemic vasodilatation. The divergent changes in the body weight, MR results, and pitting test of the nifedipine group indicates the mild peripheral edema was likely caused by an increase in the permeability of the peripheral vasculature and its fluid retention was at a much slower pace in young and healthy subjects. Modest changes in body weight and assessment of pitting may not be able to specifically indicate fluid retention at its early stage.

In summary, ^{23}Na MRI can detect fluid retention due to medications such as fludrocortisone and nifedipine at early stages.

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Reference

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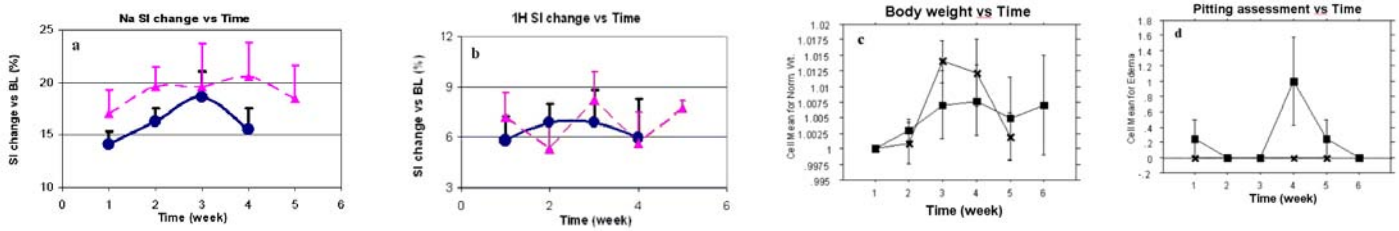

Figures **a** & **b**: ^{23}Na (**a**) and ^{1}H (**b**) MR signal changes versus time. The signal changes are referenced to the baseline visits (1 in time in **a** & **b**), calculated as (visit1+visit2)/2. Circles represent the fludrocortisone group and triangles = the nifedipine group.

Figures **c** & **d**: Normalized bodyweight (**c**) and pitting assessment (**d**) vs time/weekly visit, crosses = fludrocortisone group and squares = nifedipine group.