Original Investigation

3 Tesla ^{23}Na Magnetic Resonance Imaging During Acute Kidney Injury

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Rationale and Objectives: Sodium and proton magnetic resonance imaging (^{23}Na/^{1}H-MRI) have shown that muscle and skin can store Na^+ without water. In chronic renal failure and in heart failure, Na^+ mobilization occurs, but is variable depending on age, dialysis vintage, and other features. Na^+ storage depots have not been studied in patients with acute kidney injury (AKI).

Materials and Methods: We studied 7 patients with AKI (mean age: 51.7 years; range: 25–84) and 14 age-matched and gender-matched healthy controls. All underwent ^{23}Na/^{1}H-MRI at the calf. Patients were studied before and after acute hemodialysis therapy within 5–6 days. The ^{23}Na-MRI produced grayscale images containing Na^+ phantoms, which served to quantify Na^+ contents. A fat-suppressed inversion recovery sequence was used to quantify H_2O content.

Results: Plasma Na^+ levels did not change. Mean Na^+ contents in muscle and skin did not significantly change following four to five cycles of hemodialysis treatment (before therapy: 32.7 ± 6.9 and 44.2 ± 13.5 mmol/L, respectively; after dialysis: 31.7 ± 10.2 and 42.8 ± 11.8 mmol/L, respectively; $P > .05$). Water content measurements did not differ significantly before and after hemodialysis in muscle and skin ($P > .05$). Na^+ contents in calf muscle and skin of patients before hemodialysis were significantly higher than in healthy subjects (16.6 ± 2.1 and 17.9 ± 3.2) and remained significantly elevated after hemodialysis.

Conclusions: Na^+ in muscle and skin accumulates in patients with AKI and, in contrast to patients receiving chronic hemodialysis and those with acute heart failure, is not mobilized with hemodialysis within 5–6 days.

Key Words: Sodium; muscle; skin; magnetic resonance imaging; acute renal failure; acute renal injury; hemodialysis; therapy monitoring; 3 Tesla.

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INTRODUCTION

Sodium (Na^+) homeostasis in the body is important to blood pressure regulation, cardiovascular risk, and survival (1). However, measuring Na^+ in the body has not been possible until the development of clinical Na^+ magnetic resonance imaging (MRI) determinations. We observed earlier that Na^+ is stored without commensurate water retention in skin and muscle (2–4). The local hypertonicity resulting from Na^+ storage in skin leads to immune cell-driven induction of local tissue electrolyte clearance via modulation of cutaneous lymph capillary density (5–7). We found that disturbance of local tissue Na^+ clearance from these stores is associated with salt-sensitive increases in blood pressure. Recent findings support the theory that skin electrolyte control, by lymph capillaries, is relevant for blood pressure homeostasis (7). The findings suggest that in addition to renal compensatory mechanisms, local clearance mechanisms at the tissue level are important for tissue electrolyte homeostasis. We recently implemented a ^{23}Na-MRI modality for noninvasive detection and quantification of Na^+ reservoir metabolism in normal and hypertensive humans (8,9), in patients with hypernatremia (10), and in patients requiring chronic intermittent hemodialysis treatment (11). We used a specific coil for ^{23}Na-MRI using the upper calf as a target that allows skin and skeletal muscle to be investigated. During acute hemodialysis, the dialyzer assumes the fluid and salt-excretory function (12–19). We now investigated tissue Na^+ contents in patients with acute kidney injury (AKI) and tested the hypothesis that acute hemodialysis can mobilize Na^+ from tissue stores presumably accumulated within a few days.

AKI is typically associated with an accumulation of Na^+ (and Cl^-) in the extracellular space (20). We observed that Na^+ is deposited in skin and muscle physiologically; this occurrence is seen more often in patients with hypertension (2,4,21). The Na^+ is bound to negatively charged glycosaminoglycans. Furthermore, long-term balance studies have documented infradian rhythms in Na^+ balance and excretion that are highly consistent with an additional Na^+ storage compartment (22). We necessarily relied on animal studies

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involving carcass ashing and atomic absorption to delineate Na^+ stores (2,4–7,21). The idea of using ^{23}Na as a target for molecular (atomic) imaging to transfer such data to humans is not new (22). Recently, various applications for ^{23}Na-MRI have been reviewed (23–26). Zaaraoui et al. showed that the distribution of brain sodium accumulation is correlated with disability in multiple sclerosis (27). Ouwerkerk et al. found an increased Na^+ content in malignant breast tissue (28). Other studies concerned osteoarthritis (29) and indicated that ^{23}Na-MRI has the potential to provide insight into muscle physiology (30–35). In our previous study in patients on maintenance hemodialysis, we showed that the time course of a 4-hour hemodialysis treatment was sufficient to lower the enhanced tissue sodium content rapidly to almost control level (11). Now, our aim was to determine whether the Na^+ stored in skin and muscle tissue of patients with AKI could be reduced after acute hemodialysis therapy within the first 5–6 days. We developed ^{23}Na-MRI for our clinical purposes to study Na^+ balance in disease states (8–11,36).

MATERIALS AND METHODS

Patient Recruitment

The University Erlangen-Nürnberg committee on human subjects (Ethics Committee) approved the observational study (Re.-No. 3948). The study was conducted according to the principles of the Declaration of Helsinki. Patients with either AKI or acute on chronic renal injury were prospectively recruited from the nephrology service and the emergency department. We selected patients who could give informed consent, could clinically tolerate the procedure, could be in a supine position for at least 30 minutes, and who could be cleared for the study by a medical professional. Obviously excluded were persons with metal implants or claustrophobia. We included patients who were scheduled to receive acute hemodialysis treatment, based on their physicians' clinical judgment. Patients underwent ^{23}Na-MRI immediately before and after the guidelines-oriented acute hemodialysis therapy. We recruited healthy volunteers who were matched to the subjects with acute renal injury in a ratio of 1:2 in terms of age and gender. Healthy volunteers were recruited by advertisement and underwent ^{23}Na-MRI once. All subjects underwent medical examinations and ^{23}Na-MRI in our clinical research center.

Acute Hemodialysis Treatment

Established acute hemodialysis regimens, which employed modern hemodialysis machines from several manufacturers and high-flux dialyzers, were applied. Patients were dialyzed via a hemodialysis catheter, starting with a 1.5-hour hemodialysis treatment time on day 1. The applied treatment time was slowly extended within 2–3 days until a rhythm of 4-hour hemodialysis time every other day was achieved. Individual ultrafiltration rates were prescribed according to the patient's clinical state. Venous blood sampling and measurements of body weight and blood pressure values accompanied all pre- and post-dialytic ^{23}Na-MRI and ^{1}H-MRI measurements. All relevant hemodialysis-related parameters are presented (Table 1).

TABLE 1. Hemodialysis-related Parameters

Hemodialysis-related parameter	7 Patients with AKI
Interval MRI examinations (d)	5.6 (range: 3–8)
Number of HD treatments	4.4 (range: 3–6)
Total HD time (h)	11.5 (range: 7–18.8)
Total ultrafiltration volume (L)	8.36 (range: 2.8–17.4)
Dialysate Na^+ concentration (mmol/L)	138.1 (range: 138–141)

AKI, acute kidney injury; HD, hemodialysis; MRI, magnetic resonance imaging; Na^+, sodium.
Descriptive data of relevant hemodialysis-related parameters for the acute hemodialysis treatment of all seven patients (mean value and range).

Imaging Technique

^{23}Na-MRI for quantitative analysis was implemented, and the methods were validated and recently published (8,9). Na^+ content was measured in the lower leg muscle and skin (at the level of the largest circumference) with a custom-made ^{23}Na knee-coil (Stark Contrast, Erlangen, Germany) at 3.0 Tesla with an MRI scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany) before and after acute hemodialysis using a gradient echo ^{23}Na sequence (total acquisition time: 3.25 minutes, echo time [TE]: 2.07 ms, repetition time [TR]: 100 ms, flip angle [FA]: 90°, averages: 32, resolution: $3 \times 3 \times 30$ mm^3). The gradient echo ^{23}Na sequence was performed four times successively.

In addition, water content was quantified in tissue by ^{1}H-MRI, using a fat-suppressed inversion recovery sequence with spin density contrast (total acquisition time: 6.22 minutes, inversion time: 210 ms, TE: 12 ms, TR: 3000 ms, FA 1/2: 90°/180°, resolution: $1.5 \times 1.5 \times 5$ mm^3). A T1-weighted fast low-angle shot sequence was implemented to accurately depict the anatomy and morphology of the lower leg. The scanning protocol and the MR parameters are shown in Table 2.

Image Analysis

A radiologist interpreted the compartments of the lower leg, namely triceps surae muscle (excluding areas containing vessels) and skin (Fig 1). The different anatomical regions of interest were drawn, guided by the anatomical image (T1-weighted fast low-angle shot sequence). To measure the cutis, one pixel was marked along the coil surface. Four tubes containing aqueous solutions with increasing Na^+ concentrations (10, 20, 30, and 40 mmol/L NaCl) were positioned in a custom-made device positioned inside the coil just below the patient's lower leg (see Fig 1). Grayscale measurements of the tubes

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