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Magnetic resonance–determined sodium removal from tissue stores in hemodialysis patients

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We have previously reported that sodium is stored in skin and muscle. The amounts stored in hemodialysis (HD) patients are unknown. We determined whether ^{23}Na magnetic resonance imaging (sodium-MRI) allows assessment of tissue sodium and its removal in 24 HD patients and 27 age-matched healthy controls. We also studied 20 HD patients before and shortly after HD with a batch dialysis system with direct measurement of sodium in dialysate and ultrafiltrate. Age was associated with higher tissue sodium content in controls. This increase was paralleled by an age-dependent decrease of circulating levels of vascular endothelial growth factor-C (VEGF-C). Older (>60 years) HD patients showed increased sodium and water in skin and muscle and lower VEGF-C levels compared with age-matched controls. After HD, patients with low VEGF-C levels had significantly higher skin sodium content compared with patients with high VEGF-C levels (low VEGF-C: 2.3 ng/ml and skin sodium: 24.3 mmol/l; high VEGF-C: 4.1 ng/ml and skin sodium: 18.2 mmol/l). Thus, sodium-MRI quantitatively detects sodium stored in skin and muscle in humans and allows studying sodium storage reduction in ESRD patients. Age and VEGF-C-related local tissue-specific clearance mechanisms may determine the efficacy of tissue sodium removal with HD. Prospective trials on the relationship between tissue sodium content and hard end points could provide new insights into sodium homeostasis, and clarify whether increased sodium storage is a cardiovascular risk factor.

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Salt intake and renal excretion are related to hypertension.[1] In hemodialysis (HD) patients, the dialyzer must serve the salt-excretory function. Interdialytic salt restriction and/or removal of salt and water during HD evidently lower blood pressure levels.[2–6] However, normal blood pressure is rare in patients with end-stage renal disease (ESRD) undergoing HD despite counseling dietary salt reduction and effective body fluid management.[7–9] Recent evidence suggests that a high salt intake is associated with greater mortality in HD patients.[10] Because high interdialytic weight gain is associated with poor survival in HD patients,[11] attainment of 'normal body fluid status', expressed as 'dry weight',[12] may improve excessive mortality in HD patients and reduce cardiovascular events.[2] Despite the high profile that sodium (Na^+) and salt intake receive,[2,13,14] nephrologists are limited to monitoring serum Na^+ and dialysate Na^+ concentrations, interdialytic weight gain, and crude estimates of salt intake.

We observed that Na^+ is stored without commensurate water retention in skin and muscle.[15–17] The resulting local hypertonicity from Na^+ storage in skin leads to immune cell–driven induction of local tissue electrolyte clearance via modulation of cutaneous lymph capillary density.[18–20] 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 idea that skin electrolyte control by lymph capillaries is relevant for blood pressure homeostasis,[20] suggesting that, besides renal compensatory

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mechanisms, local clearance mechanisms at the tissue level are important for tissue electrolyte homeostasis. We recently implemented ^{23}Na magnetic resonance imaging (Na-MRI) for noninvasive detection and quantification of Na^+ reservoir metabolism in normal and hypertensive humans[21,22] and in hypernatremia.[23] We have now investigated tissue Na^+ contents in patients with ESRD and tested the hypothesis that HD can mobilize Na^+ from tissue stores. Our results in HD patients conform to our earlier observations on multicompartment Na^+ balance.[24]

RESULTS

We initially studied Na^+ and water content by Na-MRI and conventional H-MRI imaging in muscle and skin (Study 1) in 24 HD patients and in 27 age-matched healthy controls (Table 1a). Because we had shown earlier that tissue Na^+ content is primarily dependent on age in normal subjects, we separated patients and controls into two age groups (Group 1 < 60 years; Group 2 ⩾60 years).[21] Dialysis session length, ultrafiltration (UF) volumes, residual renal function as assessed by daily urine volume, and dialysate Na^+ and bicarbonate concentrations were not different between the two HD age groups (Table 1b). Age was associated with increased muscle Na^+ and skin Na^+ content in HD patients and in controls (Figure 1a). In younger patients, we found no differences in muscle ($P = 0.76$) or skin ($P = 0.31$) Na^+ content before HD treatment when compared with age-matched controls. HD treatment then reduced muscle Na^+ and skin Na^+ in these patients, resulting in lower muscle Na^+ content ($P < 0.01$) and a tendency to lower skin Na^+ ($P = 0.1$) compared with controls. In older patients, HD treatment reduced tissue Na^+ content to levels that were not different from those of controls (muscle: $P = 0.37$; skin: $P = 0.62$). Although plasma Na^+ levels were not different between HD patients and controls (Figure 1b), VEGF-C levels were significantly lower in ESRD patients than in age-matched controls. We found that older age tended to decrease VEGF-C levels in controls ($P = 0.08$) but not in ESRD patients. Skin Na^+ content continuously increased with age in our 27 control subjects with normal creatinine levels (Figure 1c). Age explained 15% of the variability in serum VEGF-C levels. The age-dependent increase in skin Na^+ content paralleled reduced tissue VEGF-C levels in the same subjects (Figure 1d). Serum VEGF-C levels further explained 17% of the variability in skin Na^+ content. Higher serum VEGF-C levels paralleled lower skin Na^+ content (Figure 1e). This finding suggests that lower VEGF-C levels occur with age, which could reduce tissue Na^+ clearance and may lead to Na^+ accumulation in the skin. Furthermore, HD patients are characterized by an anti-lymphangiogenic serum profile that may predispose the patients to tissue Na^+ accumulation.

Table 1a | Study 1. Anthropometric data of ESRD patients and controls (mean ± s.d.)

	Control		ESRD	
	<60 years ($n = 17$)	⩾60 years ($n = 10$)	<60 years ($n = 10$)	⩾60 years ($n = 14$)
Men/women	11/6	7/3	5/5	10/4
Age (years)	43.7 ± 10.5	68.9 ± 7.4[a]	42.2 ± 10.4	69.5 ± 5.6[a]
Body mass index (kg/m^2)	22.7 ± 3.5	23.8 ± 2.9	26.2 ± 5.5	25.8 ± 4.9

Abbreviation: ESRD, end-stage renal disease.
[a]$P_{(age)} < 0.001$.

Table 1b | ESRD patients and HD treatment characteristics (median, IQR)

	<60 years ($n = 10$)	⩾60 years ($n = 14$)
Diuresis (ml/day)	0, IQR 750	150, IQR 500
Dialysis vintage (years)	2.0, IQR 5	3, IQR 5
Dialysis session length (h)	4.5, IQR 1	4.5, IQR 1
Antihypertensive drugs (n)	2.0, IQR 3	3.0, IQR 2
Dialysate Na^+ (mmol/l)	138.0, IQR 3	138.0, IQR 1
Dialysate HCO_3^- (mmol/l)	32.0, IQR 4	32.0, IQR 1
Interdialytic weight gain (kg)	2.05, IQR 2.8	2.15, IQR 1.7
Ultrafiltration volume (ml)	2300, IQR 2000	2750, IQR 1050

Abbreviations: ESRD, end-stage renal disease; HD, hemodialysis; IQR, interquartile range.

To investigate the relationship between HD-enforced Na^+ removal from plasma and subsequent tissue Na^+ release, we studied Na^+ removal from skin, muscle, and blood plasma in a second study (Study 2) in 20 of our patients (Table 2a–c), who underwent HD with a batch dialysis system (Genius).[25] This system allows the monitoring of Na^+ elimination directly in ultrafiltrate and dialysate. Plasma $[K^+]$ and plasma osmolality were higher in serum than in dialysate (Table 2b), supporting clearance of blood electrolytes by diffusion. Dialysate $[Na^+]$ and plasma $[Na^+]$ were not different. HD reduced muscle Na^+ content by 27% and skin Na^+ content by 19% in the patients (Figure 2a). Na^+ removal from muscle and skin was paralleled by a reduction in water content quantified by additional H-MRI (Figure 2b). We next investigated Na^+ removal from the plasma space by HD. We calculated Na^+ removal by the dialyzer and found that calculated Na^+ removal highly correlated with Na^+ retrieval in UF and dialysate (Figure 2c). Plasma $[K^+]$ levels were successfully reduced by HD treatment (Table 2a–c). Na^+ removal was achieved by UF, whereas higher dialysate Na^+ tended to decrease plasma Na^+ removal (Supplementary Figure S1 online). Although plasma Na^+ removal by UF was achieved as predicted (Figure 2c), we did not find a similar linear relationship between measured Na^+ removal from the vascular space and tissue Na^+ removal, neither from muscle (Figure 2d) nor from skin (Figure 2e). We also found no relationship between dialysate/plasma $[Na^+]$ gradients and tissue Na^+ removal (Supplementary Figure S2 online). These findings suggest that, despite successful Na^+ removal from the blood space, the secondary clearance of Na^+ from tissue is quantitatively less predictable. The Na-MRI detection coil detects immediately below the knee joint so that skin, muscle, fat, vessels, and bone are scanned.[23] Muscle and skin Na^+ content at the lower limb was visualized and quantified relative to 1 l tissue volume by Na-MRI. Two representative examples of higher (Figure 3a) and lower (Figure 3b) Na^+ removal in