^{23}Na Magnetic Resonance Imaging-Determined Tissue Sodium in Healthy Subjects and Hypertensive Patients

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Abstract—High dietary salt intake is associated with hypertension; the prevalence of salt-sensitive hypertension increases with age. We hypothesized that tissue Na^+ might accumulate in hypertensive patients and that aging might be accompanied by Na^+ deposition in tissue. We implemented ^{23}Na magnetic resonance imaging to measure Na^+ content of soft tissues in vivo earlier, but had not studied essential hypertension. We report on a cohort of 56 healthy control men and women, and 57 men and women with essential hypertension. The ages ranged from 22 to 90 years. ^{23}Na magnetic resonance imaging measurements were made at the level of the calf. We observed age-dependent increases in Na^+ content in muscle in men, whereas muscle Na^+ content did not change with age in women. We estimated water content with conventional MRI and found no age-related increases in muscle water in men, despite remarkable Na^+ accumulation, indicating water-free Na^+ storage in muscle. With increasing age, there was Na^+ deposition in the skin in both women and men; however, skin Na^+ content remained lower in women. Similarly, this sex difference was found in skin water content, which was lower in women than in men. In contrast to muscle, increasing Na^+ content was paralleled with increasing skin water content. When controlled for age, we found that patients with refractory hypertension had increased tissue Na^+ content, compared with normotensive controls. These observations suggest that ^{23}Na magnetic resonance imaging could have utility in assessing the role of tissue Na^+ storage for cardiovascular morbidity and mortality in longitudinal studies. (***Hypertension.*** **2013;61:635-640.)** ● **Online Data Supplement**

Key Words: aging ■ gender difference ■ hypertension ■ salt ■ sodium MRI

Dietary salt intake has been investigated in relation to hypertension since the early 20th century.[1] Mendelian forms of hypertension have underscored the role of salt intake in the development of hypertension.[2] Clinicians have advised patients in terms of their dietary intake and have relied on 24 hour urine collections to verify dietary compliance.[3] Nonetheless, the results have been suboptimal. Clinicians have been limited to measuring Na^+ in plasma and urine, and the relationship to these sources for determining salt-sensitivity has been disappointing. The issue is important, as salt-sensitivity portends an earlier death.[4] Na^+ is bound to negatively charged proteoglycans that are very abundant in the skin, the body's largest organ.[5] We showed recently that signaling mechanisms exist in skin that control skin electrolyte storage.[6] When these mechanisms are perturbed, salt-sensitive hypertension results. Translating such findings to humans has been challenging. For that reason, we implemented quantitative ^{23}Na magnetic resonance imaging (^{23}Na-MRI) to visualize Na^+ in skin and soft tissues.[7] We reported on rodents measured with ^{23}Na-MRI and with MR spectroscopy, a small number of normal subjects, and 5 patients with primary aldosteronism, who were studied before and after definitive treatment. We have now extended our observations to larger numbers of normal men and women, as well as to patients with essential hypertension. We believe that ^{23}Na-MRI shows promise to be of clinical utility in further defining the relationship between salt and hypertension.

Methods

We implemented ^{23}Na-MRI for quantitative analysis in men; the methods were recently published.[7] We measured Na^+ content in lower leg muscle and skin with a ^{23}Na knee-coil (Stark-Contrast, Erlangen, Germany) at 3.0 T with a MRI scanner (Magnetom-Trio, Siemens Healthcare, Erlangen, Germany) using a 2D-FLASH sequence (total acquisition time, TA=13.7 minutes; echo time, TE=2.07 ms; repetition time, TR=100 ms; flip angle, FA=90°; 128 averages, resolution:

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3×3×30 mm^3). Four tubes containing aqueous solutions with 10, 20, 30, and 40 mmol/L NaCl served as calibration standards by relating intensity to a concentration in a linear trend analysis. In parallel, we quantified tissue water content by ^{1}H-MRI, using a fat-saturated inversion recovery sequence with spin density contrast (inversion time, TI=210 ms; TA=6.29 minutes; TE=12 ms; TR=3 s; $FA_{1/2}$=90°/180°; 128 averages, resolution: 1.5×1.5×5 mm^3), as described by other investigators.[8] Here, the 10 mmol/L NaCl tube served as a calibration standard for tissue water. We found a close linear relationship between noninvasive ^{1}H-MRI measurements and water content in porcine muscle (online-only Data Supplement Figure S1). This finding suggests that even small changes in muscle water content can be noninvasively detected with ^{1}H-MRI.

We studied normal subjects and hypertensive patients after due institutional review board's approval, according to the principles of the Declaration of Helsinki. All participants gave their written informed consent. All subjects underwent medical examinations in our clinical research center. In patients, secondary causes of hypertension had been ruled out. We measured blood pressure after 5 minutes of rest in seated position using a Dynamap pro100 oscillometric device. Three consecutive blood pressure measurements were averaged. Thereafter, a medical history was taken, and blood as well as urine samples were obtained. Subjects were defined hypertensive either if their physicians had begun antihypertensive medications, or if they displayed systolic blood pressure values ≥140 mm Hg or diastolic blood pressure values ≥90 mm Hg on examination. Refractory hypertensive patients had had elevated blood pressure (≥140 mm Hg systolic/≥90 mm Hg diastolic), despite treatment with 3 different antihypertensive drug classes that included a diuretic. Except 4 subjects treated with thyroxin for hypothyroidism, no medications were ingested in the control group. Medication characteristics of the hypertensive patients are listed in the online-only Data Supplement Table S1.

Data are expressed as mean±SD. Data were analyzed by multivariate analysis (general linear model), using SPSS software (version 19.0).

Results

We studied Na^+ content in muscle and in skin, in 57 patients with hypertension and in 56 normotensive controls, 44 women and 69 men. Water tissue content was additionally analyzed in 60 subjects, 17 hypertensive patients, and 43 normotensive controls, with conventional ^{1}H-MRI. Participants underwent no controlled dietary interventions. The ages ranged from 22 to 90 years (Table). The resulting cohort featured typical characteristics, such as increasing incidence of hypertension with age and sex-related differences. ^{23}Na-MRI images of a lower limb (immediately below the knee joint) in a 24-year-old normotensive control subject and an 85-year-old patient with hypertension, revealed striking Na^+ accumulation in the patient's skin and muscle (Figure 1A). In contrast, conventional ^{1}H-MRI (Figure 1B) of both subjects appeared similar. Because the muscle water content, as measured with ^{1}H-MRI was not different from the control, the finding suggests that Na^+ accumulation without concomitant water retention occurred.

We screened our cohort and observed age-dependent Na^+ storage in the muscle in men, whereas muscle Na^+ content was not significantly increased with age in women (Figure 2A). We found no increase in muscle water content in men, despite remarkable Na^+ storage in muscle. Interestingly, 100% increases in Na^+ content without changes in tissue water content did not lead to significant changes in serum Na^+ concentration in the same individuals (Table). Muscle water was quite constant in humans, whereas muscle Na^+ was variable.

In contrast to muscle, increasing Na^+ content paralleled increasing skin water content. With increasing age, Na^+ and water were stored in the skin in both women and men (Figures 2B and 3). When controlled for age, skin Na^+ content remained lower in women than in men (Figure 3A). A similar sex difference could be observed in skin water content (Figure 3B). Skin Na^+ and water accumulation paralleled increased systolic blood pressure in the same subjects (Figure 3C). Systolic blood pressure increased with age, and was higher in men than in women. Diastolic blood pressure in the same subjects was higher in men than in women, but did not increase with age (Figure 3D).

Our cohort included 23 men and 10 women, with a diagnosis of refractory hypertension. Refractory hypertension was associated with tissue Na^+ accumulation (Figure 4). We detected increased skin Na^+ in women with refractory hypertension compared with age-matched normotensive subjects (Figure 4A). Muscle Na^+ was significantly higher in men with refractory hypertension compared with controls (Figure 4B), whereas patients treated with spironolactone (on top of their diuretic) displayed reduced muscle Na^+ storage, and tended to have lower blood pressure (135±16 versus 147±19 mm Hg; P=0.16; Figure 4B).

Discussion

The important finding in our study is that Na^+ concentrations can be quantified noninvasively in skin and skeletal muscle in humans with ^{23}Na-MRI and that coupled with conventional ^{1}H-MRI imaging, water content can be judged simultaneously. We observed an increase in Na^+ storage with advancing age. This discovery is especially remarkable because salt-sensitivity in humans increases with age, and systolic blood pressure shows an age-dependant rise throughout all ethnic groups.[9,10] The muscle Na^+ increase was less profound in women compared with men. Na^+ deposition in muscle was not accompanied by simultaneous water accumulation, whereas in skin this state-of-affairs appeared to be the case. We could not simply distinguish normotensive from hypertensive individuals on account of Na^+ storage in either muscle or skin. However, when controlled for age, we found that patients with refractory hypertension had increased tissue Na^+ storage. We were intrigued by the preliminary observation that in patients with refractory hypertension treated with spironolactone, muscle Na^+ storage appeared to be reduced, compared with similar patients not receiving spironolactone.

Na^+ is generally assumed to be present almost exclusively in the extracellular space, with perhaps some storage in bone. Our earlier ashing studies indicated that the bone storage is minimal, and that instead large quantities are stored in the skin.[5,6] The skin is abundant in branching glycosaminoglycans that possess a strong negative charge, largely because of their sulfate content. We measured skin glycosaminoglycans content by Western blotting, and performed mRNA analysis in an earlier study.[11] We found that skin Na^+ concentration during skin Na^+ storage was 180 to 190 mmol/L. Increasing skin Na^+ coincided with increasing glycosaminoglycans content in skin.

Table. Demographic Data, Systolic and Diastolic Blood Pressue, Number of Antihypertensive Drugs, and Serum Na^+ and Creatinine Levels in the Patients

Sex	<50 Years		50–65 Years		>65 Years	
			Age (years) $P_{(age)}<0.001$; $P_{(sex)}<0.001$; $P_{(HTN)}=0.65$.			
Women	29.2±6.9 (n=15)		57.8±3.5 (n=18)		67.8±2.3 (n=11)	
Men	38.9±8.5 (n=14)		59.2±3.6 (n=26)		71.2±5.8 (n=29)	
	Control	HTN	Control	HTN	Control	HTN
Women	29.2±6.9 (n=15)	…	56.6±3.8 (n=7)	58.6±4.7 (n=11)	18.4±3.2 (n=5)	19.7±3.5 (n=6)
Men	39.2±7.9 (n=12)	37.3±15.6 (n=2)	59.7±3.8 (n=11)	58.8±3.5 (n=15)	22.2±2.4 (n=6)	22.6±4.0 (n=23)
			Systolic blood pressure (mm Hg) $P_{(age)}=0.08$; $P_{(sex)}<0.01$; $P_{(HTN)}<0.001$; $P_{(age\times HTN)}<0.05$			
Women	114±9 (n=15)		131±22 (n=18)		132±11 (n=11)	
Men	124±7 (n=14)		140±17 (n=26)		139±18 (n=29)	
	Control	HTN	Control	HTN	Control	HTN
Women	114±9 (n=15)	…	112±5 (n=7)	143±20 (n=11)	127±4 (n=5)	136±13 (n=6)
Men	124±7 (n=12)	128±6 (n=2)	126±9 (n=11)	150±14 (n=15)	126±9 (n=6)	143±19 (n=23)
			Diastolic blood pressure (mm Hg) $P_{(age)}<0.05$; $P_{(sex)}<0.05$; $P_{(HTN)}<0.05$.			
Women	74±11 (n=15)		82±12 (n=18)		74.2±8 (n=11)	
Men	79±6 (n=14)		85±8 (n=26)		81.1±10 (n=29)	
	Control	HTN	Control	HTN	Control	HTN
Women	74±11 (n=15)	…	76±6 (n=7)	87±12 (n=11)	73±7 (n=5)	75±9 (n=6)
Men	79±6 (n=12)	83±3 (n=2)	83±5 (n=11)	87±9 (n=15)	77±6 (n=6)	82±10 (n=23)
			Number of antihypertensive drugs $P_{(age)}=0.94$; $P_{(sex)}=0.76$; $P_{(HTN)}<0.001$			
Women	…		1.7±1.9 (n=18)		1.36±1.91 (n=11)	
Men	0.5±1.1 (n=13)		1.7±2.4 (n=26)		2.14±1.94 (n=29)	
	Control	HTN	Control	HTN	Control	HTN
Women	…	…	…	2.7±1.8 (n=11)	…	2.5±2.0 (n=6)
Men	…	3±0 (n=2)	…	2.9±2.5 (n=15)	…	2.7±1.8 (n=23)
			Serum Na^+ ($mmol\cdot L^{-1}$) $P_{(age)}=0.72$; $P_{(sex)}=0.23$; $P_{(HTN)}=0.65$			
Women	138.7±2.2 (n=15)		139.6±1.7 (n=18)		139.9±1.5 (n=11)	
Men	139.6±2.2 (n=12)		140.5±1.8 (n=25)		140.1±2.5 (n=29)	
	Control	HTN	Control	HTN	Control	HTN
Women	138.7±2.2 (n=15)	…	139.9±1.5 (n=7)	139.5±1.9 (n=11)	140.2±0.8 (n=5)	139.6±1.9 (n=6)
Men	139.4±1.6 (n=10)	140.8±5.3 (n=2)	140.2±1.2 (n=11)	140.7±2.1 (n=14)	139.6±2.2 (n=6)	140.2±2.6 (n=23)
			Serum Creatinine ($mg\cdot dL^{-1}$) $P_{(age)}=0.53$; $P_{(sex)}<0.001$; $P_{(HTN)}=0.16$			
Women	0.76±0.12 (n=15)		0.79±0.14 (n=18)		0.79±0.13 (n=11)	
Men	0.90±0.17 (n=12)		1.02±0.15 (n=26)		1.12±0.29 (n=29)	
	Control	HTN	Control	HTN	Control	HTN
Women	0.76±0.12 (n=15)	…	0.76±0.10 (n=7)	0.81±0.17 (n=11)	0.81±0.16 (n=5)	0.77±0.11 (n=6)
Men	0.87±0.17 (n=10)	1.05±0.02 (n=2)	0.97±0.12 (n=11)	1.06±0.17 (n=15)	1.03±0.33 (n=6)	1.14±0.29 (n=23)

HTN indicates patients with essential hypertension.
Data are mean±SD.

Dietary salt-loading coincided with increased chondroitin synthase mRNA content in the skin, whereas control markers were unchanged. The present results with ^{23}Na-MRI in humans are consistent with the animal data, and with the data from our previous ^{23}Na-MRI study; however, we cannot make definite statements on skin Na^+ concentrations in humans. Spatial resolution of ^{23}Na-MRI at 3T did not allow separate quantification of cutaneous and subcutaneous Na^+ content. As skin is thinner in men than in women, we speculate that limited resolution at 3T did not allow detection of increased skin Na^+ content in men with refractory hypertension (control: 24.1±5.6 mmol/L; patients with refractory hypertension: 26.4±4.0 mmol/L; P=0.18). Skin texture changes with aging suggested to most observers that the water content must decrease. Oh et al recently studied the issue in detail in forearm and buttocks biopsies obtained from young and old men and women. They focused on glycosaminoglycans and other constituents in dermis and epidermis, as well as water, which they measured by desiccation and weighing. The results are complex and do not follow generally preconceived notions; notably skin water does not decrease with age.[12] Future studies with additional quantitative ^{1}H-MRI measurements may elucidate to which extent skin Na^+ accumulation in humans is paralleled by commensurate water retention.[7,11]

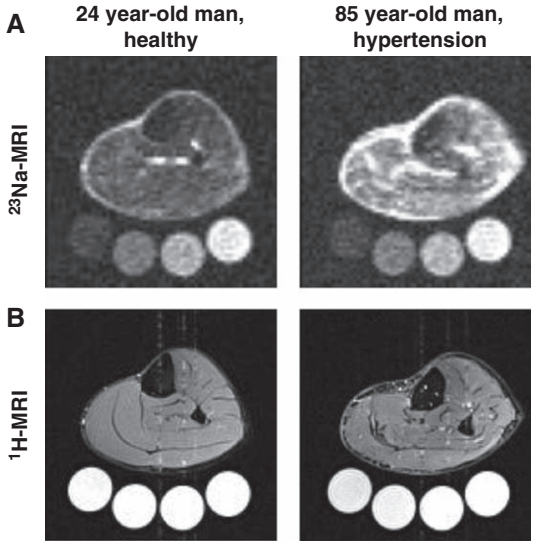

Figure 1. ^{23}Na magnetic resonance imaging (^{23}Na-MRI) of tissue Na^+. **A**, Representative ^{23}Na-MR image of the lower leg of a young normotensive man vs an older man with hypertension. Tubes with solutions containing 10, 20, 30, and 40 mmol/L of NaCl are arranged below the extremity, thereby allowing us to calibrate tissue Na^+. Tissue Na^+ content is increased in the old compared with the young subject. **B**, Tissue water in the same young and old man detected with conventional ^{1}H-MRI. No difference in muscle water content is visible to the naked eye.

Our ^{23}Na-MRI technique also indicates that Na^+ can be stored in muscle. In our earlier ashing studies, we observed substantial Na^+ deposition in muscle in the deoxycorticosterone acetate (DOCA)-salt model of rat hypertension.[13] In a subsequent study, we demonstrated that Na^+ was accumulated in muscle intracellularly, whereas intracellular K^+ concentration was decreased.[14] In a recent ^{23}Na-MRI study, we found that secondary aldosteronism was associated with pronounced muscle Na^+ accumulation in a patient with diabetes insipidus and hypernatremia.[15] We assume that similar changes occur in human skeletal muscle with age. Biopsy studies are difficult because open biopsies would have to be done on humans for technical reasons. However, such studies are feasible and planned. We appreciate the importance of increased muscle Na^+ concentrations and are aware of intracellular Na^+-sensing networks that must come into play to make adjustments maintaining normal function.[16] Our findings underscore the need to investigate the issues further.

Our results are rather counterintuitive to accepted notions. We found that Na^+ is stored in muscle tissue with age, without parallel changes in water content, and without concomitant changes in serum Na^+ or readily apparent volume expansion. We also found significant Na^+ storage in the skin. Clinical investigation of body Na^+ accumulation has traditionally been indirect, relying on estimates of extracellular water content, 24 hour urine collections, and measurements of serum Na^+ concentration. ^{23}Na-MRI provides a direct visual assessment of Na^+ storage in normal persons and hypertensive patients.

We showed previously that aldosteronism leads to water-free Na^+ storage in muscle, which can be reversed by adenoma removal or spironolactone.[7] Similarly, spironolactone may have reduced muscle Na^+ content in patients with refractory hypertension in the present study. We are aware that a prospective protocol must be performed to prove that point. A recent report underscored the ubiquitous nature of the mineralocorticoid receptor, and its role in vascular smooth muscle cell contraction.[17] Aldosterone has been shown to induce insulin resistance by increasing nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity in skeletal muscle.[18] The mineralocorticoid receptor is involved with modulating Na^+ transport. We suggest that Na^+ muscle deposition could also involve this pathway.

Perspectives

Our findings have limitations. ^{23}Na-MRI measurements at 7T will allow better discrimination of cutaneous and subcutaneous skin Na^+ content, more detailed investigation of sex differences in skin Na^+ content, and their association with hypertension. We performed cross-sectional observations in a cohort of patients and control subjects, which we plan to follow-up longitudinally within the next years to access the

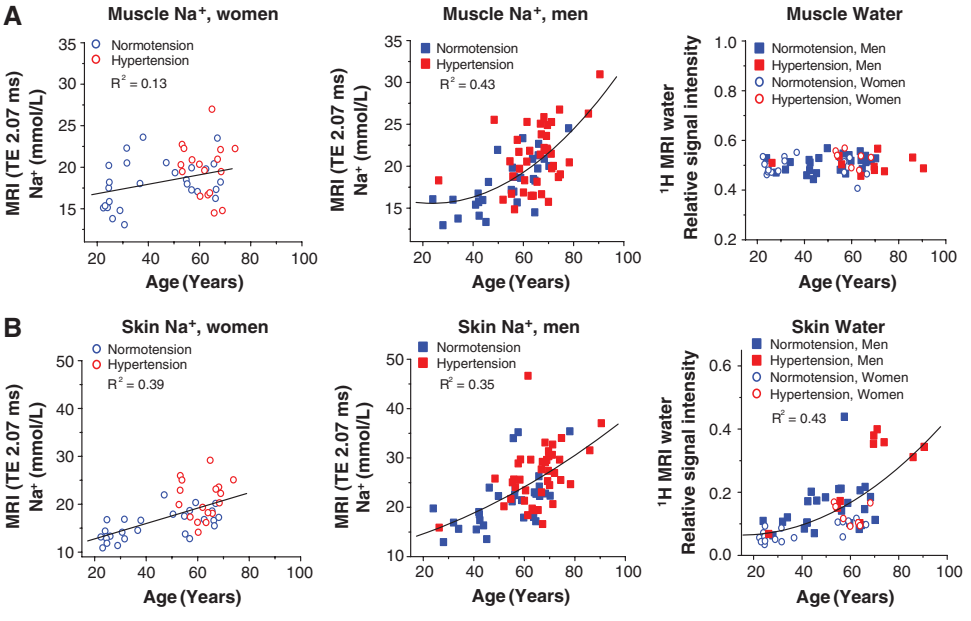

Figure 2. Tissue Na^+ and water content in relation to age. **A**, Muscle Na^+ detected by ^{23}Na magnetic resonance imaging (^{23}Na-MRI) in women (n=44, left) and men (n=69, middle) with or without the diagnosis of hypertension. Using ^{1}H-MRI, an additional analysis of muscle water content was performed in 25 women and 35 men in this study group (right panel). **B**, ^{23}Na-MRI analysis of skin Na^+ and ^{1}H-MRI measurements of skin water in the same women and men.

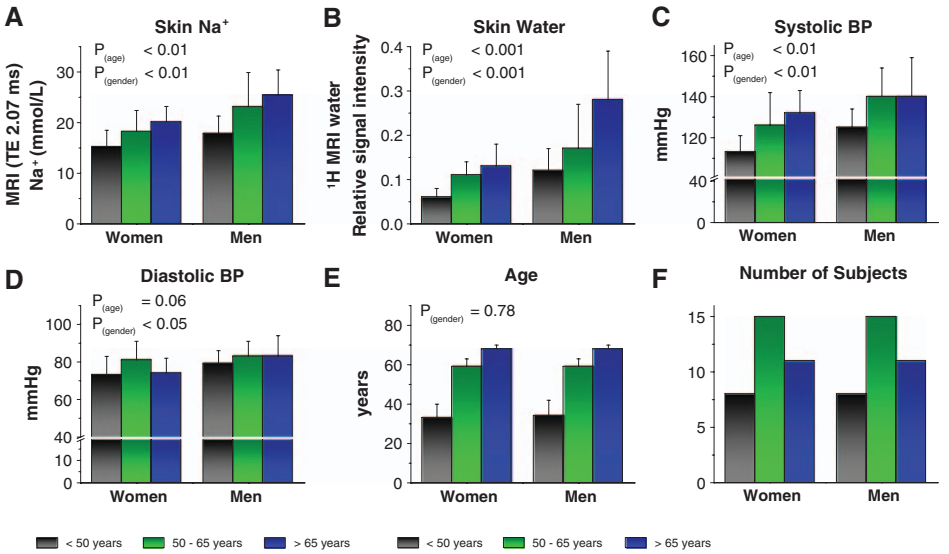

Figure 3. Increases in skin Na^+ and water content are associated with increased blood pressure. **A**, Skin Na^+ content in women and men. To visualize the increase of Na^+ with age, subjects were allocated to 3 different age subgroups (<50 years, 50–65 years, >65 years). **B**, Quantification of skin water content by ^{1}H magnetic resonance imaging (^{1}H-MRI) in the same subjects. **C** and **D**, Systolic and diastolic blood pressure in the same subjects. **E** and **F**, To test for sex differences or age, we controlled for age and sample size.

relationship between tissue Na^+ storage and cardiovascular morbidity. We performed no interventions. However, on the basis of our findings, we suggest that ^{23}Na-MRI could have clinical utility, and that such studies are justified.

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Disclosures

None.

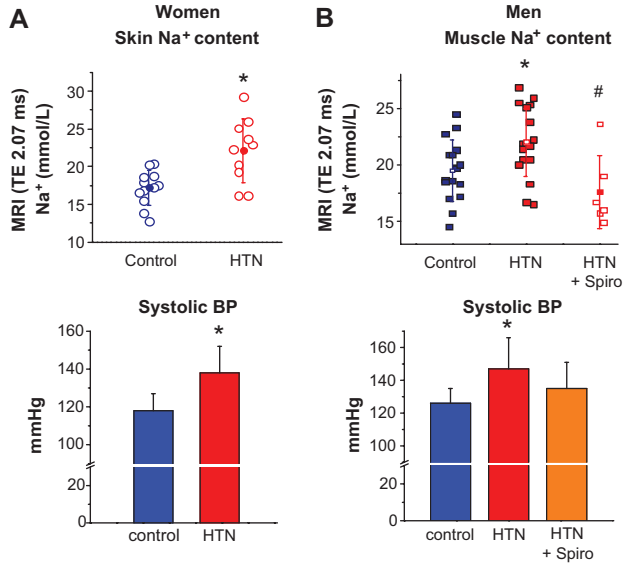

Figure 4. Tissue Na^+ content is increased in patients with refractory hypertension and lower in patients with spironolactone treatment. **A**, Skin Na^+ content in 10 women with refractory hypertension (HTN) and in controls. **B**, Muscle Na^+ content in 23 men with HTN and in controls. HTN patients without spironolactone (n=17) showed higher muscle Na^+ content than age-matched controls (n=17), whereas in refractory patients with spironolactone treatment (n=6), muscle Na^+ levels were **at the same level as controls.** *indicates $P_{(HTN)}$<0.05; and #, $P_{(spironolactone\ treatment)}$<0.05.

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Novelty and Significance

What Is New?

- This report is the first showing ^{23}Na magnetic resonance imaging (^{23}Na-MRI) applied to men and women with essential hypertension, plus normotensive control subjects.

What Is Relevant?

- We reveal that aging as well as refractory hypertension is associated with tissue Na^+ accumulation, and that Na^+ can be stored in muscle without commensurate water retention. Thus, ^{23}Na-MRI might be a tool to clinically assess states of tissue Na^+ overload, and therapy could be modified accordingly.

Summary

By using ^{23}Na-MRI, we show differences in Na^+ disposition in men and women, blood pressure-related effects, the effect of aging, and preliminary data on possible effects of spironolactone treatment.