Association Between Arterial Properties and Renal Sodium Handling in a General Population

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Abstract—Mean arterial pressure drives pressure–natriuresis and determines arterial structure and function. In a population sample, we investigated the relation between arterial characteristics and renal sodium handling as assessed by the clearance of endogenous lithium. We ultrasonographically measured diameter, cross-sectional compliance (CC) and distensibility (DC) of the carotid, brachial, and femoral arteries in 1069 untreated subjects (mean age: 41.6 years; 50.1% women; 18.8% hypertensive subjects). While accounting for covariates and standardizing for the sodium excretion rate in both sexes, CC and DC of the femoral artery increased with higher fractional distal sodium reabsorption. Differences associated with a 1-SD change in fractional distal reabsorption of sodium were 51.7 mm²/kPa×10⁻³ (95% CI: 23.9 to 79.5; P=0.0002) and 0.56×10⁻⁷/kPa (95% CI: 0.17 to 0.94; P=0.004) for femoral CC and DC, respectively. In women as well as in men, a 1-SD increment in fractional proximal sodium reabsorption was associated with decreases in femoral and brachial diameter, amounting to 111.6 µm (95% CI: 38.2 to 185.1; P=0.003) and 52.5 µm (95% CI: 10.0 to 94.9; P=0.016), respectively. There was no consistent association between the properties of the elastic carotid artery and renal sodium handling. In conclusion, higher fractional sodium reabsorption in the distal nephron is associated with higher femoral CC and DC, and higher proximal sodium reabsorption is associated with decreased brachial and femoral diameters. These findings demonstrate that there might be an influence of renal sodium handling on arterial properties or vice versa or that common mechanisms might influence both arterial and renal function. (Hypertension. 2006;48:609-615.)

Key Words: arterial stiffness ■ arterial distensibility ■ renal sodium handling ■ pressure-natriuresis

The kidneys play a central role in the pathogenesis of essential hypertension. Blood pressure starts to rise when the kidney requires a higher than usual blood pressure to maintain extracellular fluid volume within normal limits. Measuring the clearance of endogenous lithium provides a way to estimate sodium handling in the nephron. Indeed, lithium ions are freely filtered at the glomerulus and reabsorbed in the proximal tubule in parallel with sodium and water. Although lithium may be partially reabsorbed in the loop of Henle, distal tubular handling of lithium is minimal. Expressing the renal clearance of endogenous lithium as a fractional excretion provides a measure that is factored for the glomerular filtration rate. This limits possible sources of bias, such as differences in flow rate and incomplete urine collection. The fractional excretion of lithium (FELi) and fractional distal reabsorption of sodium (FNa dist) are noninvasive markers of proximal tubular sodium handling and the proportion of sodium escaping reabsorption in the proximal tubule that is not eliminated in the urine, respectively.1

Mean arterial pressure drives pressure-natriuresis and influences arterial structure and function. The renin–angiotensin–aldosterone system is an important determinant of renal sodium handling and the properties of the arterial wall. To our knowledge, no previous study addressed the relation between renal sodium handling and arterial properties while accounting for the activity of the renin–angiotensin–aldosterone system. Therefore, in the framework of the Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO), we investigated the functional and structural properties of 3 large arteries in relation to renal sodium handling as assessed by the clearance of endogenous lithium. We also measured plasma renin activity and the urinary aldosterone excretion rate.

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Methods

Study Population
The FLEMENGO 2 is part of the European Project on Genes in Hypertension (EPOGH). From August 1985 until July 2003, we recruited a random sample of families from a geographically defined area in Northern Belgium. The Ethics Committee of the University of Leuven approved the study. All of the participants or their parents gave informed written consent. The participation rate averaged 64.3%.

Of 1306 participants who underwent a vascular ultrasound examination, 1291 (98.9%) had high-quality measurements available at the 3 target arteries, and 1278 (97.9%) also underwent an assessment of renal sodium handling by measurement of the clearance of endogenous lithium. Of these 1278 subjects, we excluded 36 because of renal sodium handling by measurement of the clearance of endogenous lithium. Of these 1278 subjects, we excluded 36 because of a very high lithium concentration in serum (≥1.0 μmol/L) or urine (≥20 μmol/L), suggestive of external contamination, 14 because of missing questionnaire data, and 159 because of current intake of antihypertensive drugs. Thus, the number of subjects analyzed totaled 1069.

Clinical Measurements
For ≥3 hours before the examination, the participants refrained from heavy exercise, smoking, and alcohol or caffeine-containing beverages. Trained nurses measured the subjects’ anthropometric characteristics and blood pressure. They administered a questionnaire to collect information about each participant’s recent medical history, smoking and drinking habits, and intake of medications. Each subject’s blood pressure was the average of 5 consecutive readings measured at the clinic after ≥5 minutes of sitting rest. Mean arterial pressure was diastolic pressure plus one third of pulse pressure. Hypertension was a blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic. Body mass index was weight in kilograms divided by the square of height in meters.

Vascular Measurements
By means of a pulsed ultrasound wall-tracking system (Wall Track System; Pie Medical), 3 trained researchers obtained vascular measurements at the common carotid artery 2 cm proximal of the carotid bifurcation into the profound and superficial branches, and at the right brachial artery 2 cm proximal of the antecubital fossa. During the ultrasound examination, an automated oscillographic device (Dinamap 845; Critikon Inc) recorded blood pressure at the upper arm at 5-minute intervals. As for the conventional auscultatory measurements, cuff size was adjusted to the circumference of the upper arm. Standard cuffs had an inflatable bladder of 12×24 cm. As described elsewhere, the observers used application tonometry with a pencil-shaped probe (Millar Instruments Inc) and calibration to mean arterial pressure and diastolic blood pressure at the brachial artery to derive the local pulse pressure at the other arteries. We computed cross-sectional compliance (CC) and the distensibility coefficient (DC) from the diastolic cross-sectional area (A), the systolic increase in cross-sectional area (∆A), and the local pulse pressure (PP): CC = ∆A/PP and DC = (∆A/A)/PP. A and ∆A were calculated from diameter (D) and the change in diameter (ΔD) as A = π/4(D/2)² and ∆A = π/4[(D + ΔD)/2)² - π/4(D/2)², respectively. The intraobserver intrasession variability was <10% for the carotid measurements, <5% for the brachial and femoral diameter, and amounted to 10% to 15% for brachial and femoral CC and DC. The intraobserver intersession and interobserver intrasession variability were of the same order of magnitude.

Renal Sodium Handling
On the day of the vascular measurements, venous blood samples were drawn to measure the serum concentrations of sodium, lithium, and creatinine and plasma renin activity. The participants also collected an exactly timed urine sample over 4 to 6 hours to measure the excretion of sodium, lithium, creatinine, and aldosterone. We measured the sodium concentration in serum and urine by flame photometry and serum and urinary creatinine by an automated enzymatic method. We determined plasma renin activity (RIA-0180, DRG Instruments GmbH) and the urinary aldosterone concentration (DSL-8600 Active, Diagnostic Systems Laboratories, Inc) by radioimmunoassay, according to the instructions provided by the manufacturers of the analytic kits. Endogenous trace lithium was measured with an electrothermal atomic absorption spectrophotometer (model AAS 300) with an HGA-700 graphite furnace (Perkin-Elmer Inc). Clearances (C) were calculated as Cx = Ux × V/Pr, where Ux and Pr are the urinary and plasma concentrations of the solute x, and V is the volume of the urine sample. We computed the fractional excretion of sodium (FEna) and lithium (FELi) by dividing the sodium (Cna) and lithium (Cl) clearances by the creatinine clearance. We expressed these ratios as a percentage. RNax was estimated as [(FEna - FEna)/FEna]×100. RNax is a measure of the amount of sodium that escapes reabsorption in the proximal tubules and is reabsorbed in the postproximal tubules. We defined the fractional proximal sodium reabsorption (RNaprox) as 100 - FEna.

Statistical Analysis
For database management and statistical analysis, we used SAS software (SAS Institute), version 9.1. We normalized the distributions of plasma renin activity and the aldosterone excretion rate by a logarithmic transformation. We report the central tendency and spread of these measurements as the geometric mean and the interquartile range, respectively. We compared means and proportions using the large sample z test and Fisher’s exact test, respectively. Our statistical methods also included single and multiple linear regression. We searched for possible covariates of the arterial and renal phenotypes, using stepwise multiple regression, with the P value for independent variables to enter and stay in the model set at 0.15. Covariates considered for entry into the model were observer, age, body mass index, pulse rate, mean arterial pressure, current smoking, and alcohol intake. We initially analyzed women and men separately, but we combined both sexes when the interaction terms between explanatory variables and sex were nonsignificant (P>0.15). We standardized RNax and RNaprox to the mean sodium excretion rate for the whole study population (8.3 mmol/h).

Results
Characteristics of the Participants
Women and men had similar age (mean: 41.6 years; range: 10.9 to 81.5 years). Table 1 summarizes their demographic characteristics. The study sample included 201 (18.8%) hypertensive patients not taking any antihypertensive medication. Fewer women than men reported smoking or alcohol intake. Of the 535 women and 534 men, 146 women (27.3%) and 176 men (33.0%) were smokers, and 166 women (31.0%) and 326 men (61.0%) reported intake of alcohol. In smokers, median tobacco use was 15 cigarettes per day (interquartile range: 8 to 23 cigarettes per day). In drinkers, the median alcohol consumption was 16 g per day (interquartile range: 8 to 30 g per day). Among women, 171 (32.0%) reported natural or surgical menopause, whereas 123 (23.0%) used oral contraceptives, and 7 (1.3%) took hormonal replacement therapy.

Arterial Properties
Table 2 gives the vessel wall properties by sex and vascular territory. Across the 3 vascular territories, arterial diameter, CC, and local PP were consistently smaller (P<0.0002) in women than in men, whereas the opposite was the true for DC (P<0.0007).

Renal Measurements
The excretion rate of sodium, lithium, and creatinine and creatinine clearance were significantly lower in women than
in men (Table 1). Compared with women, men had higher \( FE_{Na} \), whereas the opposite was true for \( RN_{dist} \) (Table 1). 

\( RN_{prox} \) changed curvilinearly with age, whereas \( RN_{dist} \) decreased after middle age (Figure). The sodium excretion rate was a strong and independent determinant of \( FE_{Na} \), whereas the opposite was true for \( RN_{dist} \) (Table 1). Compared with women, men had higher \( RN_{prox} \), and \( RN_{dist} \) (Table 3). In all of the further analyses, we, therefore, standardized \( RN_{prox} \) and \( RN_{dist} \) to the average excretion rate of sodium in the whole study population (8.3 mmol/h).

Both before and after adjustment for age, body mass index, pulse rate as index of sympathetic modulation, and mean arterial pressure, plasma renin activity was positively and independently associated with \( RN_{dist} \) in men. A 1-SD increase in \( RN_{dist} \) (3%) was associated with an increase in plasma renin activity by 0.132 ng/mL per hour (95% CI: 0.065 to 0.198; \( P = 0.0001 \)). In women, but not men, the aldosterone excretion rate was significantly associated with \( RN_{prox} \) (Table 4) with a 1-SD increase in \( RN_{prox} \) (10%) resulting in a decrease in urinary aldosterone by 0.097 ng/mL (95% CI: 0.031 to 0.162; \( P = 0.004 \)).

**Vessel Wall Properties in Relation to Renal Sodium Handling**

Stepwise multiple regression analysis showed significant and independent associations between arterial property and age, body mass index, mean arterial pressure, pulse rate, smoking, and alcohol intake. We, therefore, adjusted our further analyses for these covariates and additionally also for observer. In analyses combining women and men, we also adjusted for sex.

In both sexes, the CC and the DC of the femoral artery significantly increased with higher \( RN_{dist} \). The \( RN_{dist} \)-by-sex interaction terms for these associations were nonsignificant (\( P > 0.63 \)), indicating consistent results in women and men. In all 1069 of the subjects combined, a 1-SD increment in

**TABLE 1. Characteristics of Participants by Sex**

| Characteristics       | Women (n=535) | Men (n=534) | \( P \) |
|-----------------------|---------------|-------------|--------|
| Anthropometry         |               |             |        |
| Age, y                | 41.2±14.7     | 42.1±14.5   | 0.32   |
| Body mass index, kg/m²| 24.3±4.2      | 25.4±3.7    | <0.0001|
| Systolic pressure, mm Hg | 122.1±14.9   | 128.0±13.1  | <0.0001|
| Diastolic pressure, mm Hg | 76.6±9.9     | 81.0±10.4   | <0.0001|
| Mean arterial pressure, mm Hg | 91.8±10.7   | 96.7±10.1   | <0.0001|
| Pulse pressure, mm Hg | 44.8±11.1     | 48.3±11.9   | <0.0001|
| Hypertensive, n (%)   | 72 (13.5)     | 129 (24.2)  | <0.0001|
| Serum biochemistry    |               |             |        |
| Sodium, mmol/L        | 141.0±3.3     | 142.6±2.4   | <0.0001|
| Lithium, μmol/L       | 0.17±0.08     | 0.19±0.10   | 0.009  |
| Creatinine, μmol/L    | 73.5±12.7     | 90.4±14.0   | <0.0001|
| Plasma renin activity, ng/mL | 0.43 (0.20 to 0.86) | 0.43 (0.22 to 0.87) | 0.79   |
| Urinary excretion rate|               |             |        |
| Sodium, mmol/h        | 7.1±5.4       | 9.4±6.6     | <0.0001|
| Lithium, μmol/h       | 0.17±0.13     | 0.22±0.17   | <0.0001|
| Creatinine, mmol/h    | 0.41±0.31     | 0.61±0.37   | <0.0001|
| Aldosterone, nmol/h   | 1.01 (0.51 to 2.02) | 0.98 (0.57 to 1.77) | 0.43   |
| Renal function        |               |             |        |
| Creatinine clearance, mL/min | 87.3±24.8   | 105.9±32.0  | <0.0001|
| \( FE_{Na} \), %      | 0.92±0.44     | 1.00±0.45   | 0.006  |
| \( RN_{prox} \), %    | 79.3±8.4      | 79.5±8.3    | 0.64   |
| \( RN_{dist} \), %    | 95.0±3.1      | 94.6±3.2    | 0.02   |

Values are mean±SD, geometric mean (interquartile range), or No. (%) of subjects.

**TABLE 2. Arterial Characteristics by Sex**

| Characteristics          | Women (n=535) | Men (n=534) |
|--------------------------|---------------|-------------|
| Common carotid artery    |               |             |
| Diameter, μm             | 6732±735      | 7498±842    |
| Pulse pressure, mm Hg    | 44.8±11.1     | 48.3±11.9   |
| CC, mm²/kPa              | 1.01±0.45     | 1.12±0.47   |
| DC, 10⁻³kPa              | 29.0±14.1     | 25.6±11.0   |
| Brachial artery          |               |             |
| Diameter, μm             | 3892±705      | 4807±697    |
| Pulse pressure, mm Hg    | 45.3±8.9      | 50.0±9.9    |
| CC, mm²/kPa              | 0.15±0.11     | 0.19±0.15   |
| DC, 10⁻³kPa              | 13.2±11.3     | 11.4±10.0   |
| Femoral artery           |               |             |
| Diameter, μm             | 8485±1126     | 10003±1346  |
| Pulse pressure, mm Hg    | 49.4±12.0     | 53.6±12.1   |
| CC, mm²/kPa              | 0.67±0.40     | 0.77±0.48   |
| DC, 10⁻³kPa              | 12.0±7.0      | 9.9±5.7     |

Values are mean±SD. All sex differences were statistically significant (\( P < 0.0007 \)).
RNA$_{\text{prox}}$ (3%) was associated with an increase in femoral CC by $51.7 \text{ mm}^2/\text{kPa} \times 10^{-3}$ (95% CI: 23.9 to 79.5; $P=0.0002$) and with an increase in femoral distensibility by $0.56 \times 10^{-3}/\text{kPa}$ (95% CI: 0.17 to 0.94; $P=0.004$). In women as well as in men, the diameter of the brachial and femoral arteries decreased with higher RNA$_{\text{prox}}$, whereas the diameter of the carotid artery increased with higher RNA$_{\text{dist}}$ in men but not in women (Table 5).

Both before and after adjustment for age, body mass index, pulse rate, smoking, and alcohol intake, there was in women, as well as in men, an inverse association of mean arterial pressure and diastolic blood pressure with RNA$_{\text{prox}}$ (Table 4). An $\approx 1$-SD increase in RNA$_{\text{prox}}$ (10%) was associated with a decrease in mean arterial pressure by 0.95 mm Hg (95% CI: 0.42 to 1.49; $P=0.0005$) and a decrease in diastolic blood pressure by 1.13 mm Hg (95% CI: 0.59 to 1.66; $P=0.0009$).

Sensitivity analyses produced consistent results. After exclusion of 130 women taking oral contraceptives or on hormonal replacement therapy, adjusted effect sizes associated with a 1-SD increase in RNA$_{\text{prox}}$ were 49.2 μm (95% CI: 6.7 to 91.6; $P=0.025$) and 107.5 μm (95% CI: 32.4 to 182.6; $P=0.005$) for the decreases in the brachial and femoral diameters, respectively. After we had excluded 301 women with an active menstrual cycle, the corresponding effect sizes were $51.7 \text{ mm}^2/\text{kPa} \times 10^{-3}$ (95% CI: 24.0 to 79.5; $P=0.0002$) and $0.55 \times 10^{-3}/\text{kPa}$ (95% CI: 0.17 to 0.94; $P=0.004$) for the increases in femoral CC and DC and 52.5 μm (95% CI: 10.0 to 94.9; $P=0.016$) and 111.6 μm (95% CI: 38.2 to 185.1; $P=0.0027$) for the decreases in brachial and femoral diameters, respectively. Finally, our results also remained consistent after exclusion of subjects $<20$ years of age. The aforementioned estimates then were $52.4 \text{ mm}^2/\text{kPa} \times 10^{-3}$ (95% CI: 24.6 to 80.2; $P=0.0003$) and $0.65 \times 10^{-3}/\text{kPa}$ (95% CI: 0.26 to 1.03; $P=0.0009$) for femoral compliance and distensibility and 63.3 μm (95% CI: 19.2 to 107.3; $P=0.005$) and 132.4 μm (95% CI: 55.7 to 209.0; $P=0.0007$) for the brachial and femoral diameters, respectively.

### Discussion

The key finding of our study was that while accounting for covariates and standardizing for the sodium excretion rate, the CC and DC of the femoral artery increased with higher distal sodium reabsorption, whereas the brachial and femoral diameters lessened with higher proximal sodium reabsorption. To our knowledge, no previous study addressed the possible influence of renal sodium handling on arterial properties or, conversely, the possible effects of arterial characteristics on renal sodium handling.

According to Guyton’s hypothesis, the pathogenesis of hypertension, irrespective of the primary causal factor, always involves the pressure–natriuresis relation in the kidney, with higher pressures being required to excrete a given sodium load. In keeping with this concept, we found an inverse and independent relation of RNA$_{\text{prox}}$ with mean arterial pressure and diastolic blood pressure. Higher mean arterial pressure is associated with elevated renal interstitial hydrostatic pressure and, therefore, elevated sodium reabsorption.

### TABLE 3. Determinants of Renal Sodium Handling

| Determinants | $FE_{\text{Na}}$ | RNA$_{\text{prox}}$ | RNA$_{\text{dist}}$ |
|--------------|----------------|---------------------|-------------------|
| $R^2$        | 0.306          | 0.046               | 0.383             |
| Intercept    | 0.34†          | 90.9†               | 97.0†             |

Partial regression coefficient±SE:

| Age (year$\times 10^{-3}$) | 3.46±0.89† | $-387.3\pm86.7$† | $-11.8\pm5.9$* |
| Age squared (year$^2\times 10^{-3}$) | NC         | 4.10±0.97†       | NC               |
| Body mass index, kg/m$^2$   | $-0.010\pm0.003$† | 0.149±0.071*      | 0.041±0.020*     |
| Mean arterial pressure, mm Hg | 0.0043±0.0013† | $-0.089\pm0.028$† | NS               |
| Female gender (0, 1) | NS         | NS                 | $-0.35\pm0.16$*  |
| Sodium excretion rate, mmol/h | 0.039±0.002† | 0.117±0.042†      | $-0.374\pm0.015$† |
| Current smoker (0, 1) | $-0.068\pm0.025$† | 1.388±0.560*     | NS               |

NC indicates that age squared was not considered.

Significance of the partial regression coefficients: NS, $P>0.15$; *$P<0.05$; and †$P<0.01$. 

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**FIGURE**

FE$_{\text{Na}}$, RNA$_{\text{prox}}$, and RNA$_{\text{dist}}$ by age. Values are mean±SE. The number of subjects contributing to the means is given for each age group.
with less sodium reabsorption in the proximal tubules, which are responsible for reuptake of 80% of the filtered sodium load.\textsuperscript{7} Our cross-sectional epidemiologic study cannot directly address the mechanisms underlying the positive relation of femoral compliance and distensibility with RNadist. A possible explanation might be that a common mechanism, operating in both the arterial wall and the renal tubules, might influence arterial properties and renal sodium handling. For instance, genetic variability in ion transport across cell membranes might be involved. In the present population, we demonstrated previously that mutations of the cytoskeleton protein \(\alpha\)-adducin (460 Gly \(\rightarrow\) Trp) and the angiotensin-converting enzyme (ACE I\(\rightarrow\)D) jointly predicted the incidence of hypertension.\textsuperscript{8} In cross-sectional analyses of the same population, we also noticed that the combination of these 2 functional mutations\textsuperscript{9,10} was associated with raised serum

| Location        | Variable            | Group | Estimate (95% CI) | \(P\)  |
|-----------------|---------------------|-------|-------------------|--------|
| Carotid artery  | Diameter, \(\mu\)m  | All   | 10.0 (32.5 to 52.5) | 0.63   |
|                 |                     | Men   | 72.9 (11.0 to 134.8) | 0.021  |
|                 |                     | Women | 5.6 (61.6 to 50.3) | 0.84   |
|                 | Pulse pressure, mm Hg | All  | 0.04 (−0.68 to 0.77) | 0.91   |
|                 |                     | Men   | 0.07 (−0.67 to 0.81) | 0.85   |
|                 |                     | Women | 2.5 (−33.9 to 28.8) | 0.87   |
|                 | Compliance, \(\text{mm}^2/\text{kPa} \times 10^{-3}\) | All  | −12.6 (−40.0 to 12.0) | 0.32   |
|                 |                     | Men   | 39.8 (2.6 to 76.9) | 0.037  |
|                 |                     | Women | 0.15 (−0.38 to 0.68) | 0.57   |
|                 | Distensibility coefficient, \(10^{-3}/\text{kPa}\) | All  | 0.29 (−0.50 to 1.08) | 0.47   |
|                 |                     | Men   | −0.33 (−0.99 to 0.33) | 0.33   |
|                 |                     | Women | 0.15 (−0.38 to 0.68) | 0.57   |
| Brachial artery | Diameter, \(\mu\)m  | All   | −52.6 (−94.9 to −10.0) | 0.016  |
|                 |                     | Men   | 32.8 (−9.8 to 75.5) | 0.13   |
|                 | Pulse pressure, mm Hg | All  | −0.07 (−0.67 to 0.52) | 0.81   |
|                 |                     | Men   | −0.47 (−1.07 to 0.13) | 0.13   |
|                 |                     | Women | 9.7 (−17.1 to −2.4) | 0.010  |
|                 | Compliance, \(\text{mm}^2/\text{kPa} \times 10^{-3}\) | All  | 5.8 (−0.7 to 12.4) | 0.085  |
|                 |                     | Men   | −0.3 (−10.2 to 9.5) | 0.95   |
|                 |                     | Women | −0.56 (−1.08 to −0.05) | 0.031  |
| Femoral artery  | Diameter, \(\mu\)m  | All   | −111.6 (−185.1 to −38.2) | 0.003  |
|                 |                     | Men   | 67.5 (−6.1 to 141.0) | 0.071  |
|                 | Pulse pressure, mm Hg | All  | 0.35 (−0.44 to 1.13) | 0.38   |
|                 |                     | Men   | −0.11 (−0.89 to 0.67) | 0.78   |
|                 | Compliance, \(\text{mm}^2/\text{kPa} \times 10^{-3}\) | All  | −27.7 (−62.3 to 6.9) | 0.11   |
|                 |                     | Men   | 51.7 (23.9 to 79.5) | 0.0002 |
|                 | Distensibility coefficient, \(10^{-3}/\text{kPa}\) | All  | −0.06 (−0.62 to 0.51) | 0.84   |
|                 |                     | Men   | −0.55 (−1.07 to −0.04) | 0.034  |

\(\text{RNaprox}\) and \(\text{RNadist}\) represent the fractional sodium reabsorption along the proximal and postproximal tubules, respectively. \(\text{RNaprox}\) and \(\text{RNadist}\) were standardized to a sodium excretion rate of 8.3 mmol/h. Regression coefficients were adjusted for observer, age, mean arterial pressure (not for pulse pressure as dependent variable), pulse rate, body mass index, smoking, and alcohol intake. \(P\) refers to the significance of the partial regression coefficients. We reported results for women and men separately, if the \(P\) value for the interaction term between the indexes of renal sodium handling and sex was <0.15.
creatinine concentration,11 increased femoral intima–media thickness,12 and 24-hour proteinuria.11 In this context, it is conceivable that the constitutive activation of the sodium pump in the α-adducin Ttp allele carriers not only occurs in renal tubular cells but that it might also be present in vascular smooth muscle cells. In vascular myocytes, enhanced Na⁺/K⁺-ATPase activity might reduce the sarcolemmal Na⁺/Ca²⁺ exchange and through calcium-dependent pathways modulate excitation–contraction coupling.13

Oxidative stress might represent another common pathway, which potentially affects both arterial and renal function. Indeed, studies in patients with end-stage renal disease demonstrated that asymmetrical dimethylarginine (ADMA), an endogenous competitive inhibitor of NO synthase, behaves as an independent risk factor associated with endothelial dysfunction, arterial stiffening, carotid atherosclerosis, and the risk of cardiovascular events.14 In patients with essential hypertension15 and in salt-sensitive Dahl rats,16 sodium loading increases,15,16 whereas salt depletion decreases,15 the plasma levels of ADMA. In healthy men, infusion of ADMA increased renovascular resistance and lowered effective renal plasma flow, as well as sodium excretion and FE₅₀.17

In women and men, we noticed a negative relation between the brachial and femoral diameters and RNα₉. Vasocostriction is the hallmark of hypertension. Animal models of hypertension,18 hypertensive patients,19 normotensive subjects with 1 first-degree relative with hypertension,20 and patients with white-coat hypertension19 have higher RNα₉. Moreover, Draaijer et al21 reported a significantly lower arterial compliance in sodium-sensitive than in sodium-resistant men with borderline hypertension, independent of cardiac output, blood pressure, and hormonal factors. Along similar lines, salt sensitivity rather than salt intake seems to be a more important determinant of the mechanical properties of the carotid arteries in Dahl rats.22

In women, the aldosterone excretion rate was negatively associated with RNα₉, whereas in men there was a positive association between plasma renin activity and RNα₉. These relations are physiologically plausible. Indeed, enhanced proximal sodium reabsorption leads to inhibition of the renin–angiotensin–aldosterone system. Conversely, under conditions requiring sodium conservation, the distal tubule is the ultimate target of the activated renin system. Heterogeneity in the study population or residual confounding might explain why these relations were not consistent in women and men. For instance, our analysis did not take salt sensitivity into account, the prevalence of which is ≈26% in normotensive subjects and ≈51% in hypertensive patients.23 Furthermore, there might be physiological differences between women and men in renal sodium handling. Progesterone binds to the human mineralocorticoid receptor with nearly the same affinity as aldosterone.24 Progesterone and its metabolites antagonize aldosterone.25 The renal tubular response to a sustained increase in sodium intake was similar in women during the follicular phase of their cycle compared with men. In contrast, in women examined during the luteal phase of their menstrual cycle, increasing sodium intake led to a marked sodium escape from the distal nephron, with no change in proximal sodium reabsorption.26 We did not record the phase of the menstrual cycle, but our results remained consistent after we excluded from analysis women taking oral contraceptives or hormonal replacement therapy or those with an active menstrual cycle.

The central elastic arteries, such as the carotid artery, and the more peripheral muscular conduit vessels, including the brachial and femoral arteries, have different properties.27 Going from the central to the peripheral arteries, the collagen/elastin ratio reverses, vascular smooth muscle cells become the predominant component of the arterial wall, and the phenotype of the vascular smooth muscle cells changes.27 In line with this diversity along the arterial tree, we earlier noticed that genetic influences on the CC and DC of large arteries depended on vascular territory.28 In clinical trials,29,30 diuretics decreased the carotid but not the brachial and femoral diameters, and they increased brachial and femoral but not carotid distensibility. Finally, the relation between arterial stiffness and body mass index is more complex in the carotid than muscular arteries, because carotid properties in relation to body mass index vary according to sex and age.2 These observations27–30 help to understand the heterogeneity in the current associations of arterial properties with renal sodium handling.

The present study must be interpreted within the context of its limitations. The endogenous lithium clearance provides only an indirect measurement of renal tubular sodium transport in vivo. The fractional excretion of sodium and the creatinine clearance, which we used to standardize data, showed large interindividual variability. Although the measurement of trace lithium in biological fluids at concentrations down to 0.03 μmol/L shows intraday and interday variation of <10%,31 the intraindividual variability in RNα₉ and RNα₉ on repeated measurement must be large, mirroring the day-to-day variation in the 24-hour urinary sodium excretion.32 However, large variability would rather tend to weaken than strengthen the observed relations of the indexes of renal sodium handling with femoral compliance and distensibility and the brachial and femoral diameters.

Perspectives

The novel finding in our study is the significant association between arterial properties and renal sodium handling. If confirmed, our findings might be relevant for unraveling the pathogenesis of essential hypertension and its renal and vascular complications. We will further explore to what extent genetic variability in the regulation of sodium homeostasis, in particular, the adducin polymorphisms,33 contributed to the present findings.

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Disclosures

None.

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