Angiotensin-converting enzyme inhibitors and angiotensin-II-receptor antagonists modulate sodium handling based on endogenous lithium clearance

Marcin Cwynar[1], Katarzyna Stolarz-Skrzypek[2], Jerzy Gąsowski[1], Barbara Wizner[1], Wiktoria Wojciechowska[2], Agnieszka Olszanecka[2], Barbara Gryglewska[1], Anna Dzieża-Grudnik[1], Adam Bednarski[2], Mirosław Krośniak[3], Henryk Bartoń[3], Kalina Kawecka-Jaszcz[2], Marek Rajzer[2], Tomasz Grodzicki[1]

[1]Department of Internal Medicine and Gerontology, Jagiellonian University Medical College, Kraków, Poland
[2]1st Department of Cardiology, Interventional Electrocardiology and Hypertension, Jagiellonian University Medical College, Kraków, Poland
[3]Trace Element Research Laboratory, Department of Food Chemistry and Nutrition, Faculty of Pharmacy, Jagiellonian University Medical College, Kraków, Poland

Correspondence to:
Marcin Cwynar MD, PhD, Department of Internal Medicine and Gerontology, Jakubowskiego 2, 30–688 Kraków, Poland,
phone: +48 12 400 29 00
e-mail: marcincw@poczta.onet.pl

DOI: 10.33963/v.kp.98723

Received:
November 3, 2023

Accepted:
December 29, 2023

Early publication date:
January 9, 2024

ABSTRACT

Background: Numerous studies based on assessment of lithium clearance demonstrated higher sodium reabsorption in renal proximal tubules in individuals with hypertension, overweight, obesity, metabolic syndrome, or diabetes.

Aims: We aimed to assess the influence of angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin-II-receptor antagonists (ARB) treatment on sodium handling.

Methods: In a sample of 351Caucasian subjects without diuretic treatment with prevailing sodium consumption, we studied associations between renal sodium reabsorption in proximal (FPR_{Na}) and distal (FDR_{Na}) tubules assessed by endogenous lithium clearance and daily sodium intake measured by 24-hour excretion of sodium ($U_{Na}V$), in the context of obesity and long-term treatment with ACE-I or ARB.

Results: In the entire study population, we found a strong negative association between FPR_{Na} and ACE-I/ARB treatment (b = –19.5; SE = 4.9; P <0.001). Subjects with FPR_{Na} above the median value showed a significant adverse association between FPR_{Na} and age (b = –0.06; SE = 0.02; P = 0.003), with no association with ACE-I/ARB treatment (P = 0.68). In contrast, in subjects with FPR_{Na} below the median value, we found a strongly significant adverse relationship between FPR_{Na} and ACE-I/ARB treatment (b = –30.4; SE = 8.60; P <0.001), with no association with age (P = 0.32).

Conclusions: ACE-I/ARB long-term treatment modulates FPR_{Na} in the group with lower reabsorption, but not in that with higher than median value for the entire study population.

Key words: ACE-I/ARB treatment, endogenous lithium clearance, sodium handling

INTRODUCTION

Sodium handling is characterized by osmolite excretion with anti-parallel water reabsorption that is achieved through interactions of multiple factors and undergoes complex regulation. Lithium ions undergo filtration in renal glomeruli, while their reabsorption takes place almost exclusively in proximal tubules. Because transporting lithium through cellular membranes involves the same mechanisms as transporting sodium and water, lithium clearance is a very accurate marker of fractional sodium reabsorption in renal tubules. High lithium clearance indicates a better ability to excrete sodium from the corresponding tubule [1]. Numerous studies based on assessment of lithium clearance demonstrated higher sodium reabsorption in renal proximal tubules in individuals with hypertension, overweight, obesity, metabolic syndrome, or diabetes [2–4]. Among the factors influencing sodium handling, the impact of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin-II-receptor antago-

WHAT'S NEW?

In a large group of Caucasian subjects without diuretic treatment, we demonstrated associations between long-term treatment with angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin-II-receptor antagonists (ARB) and renal sodium reabsorption in proximal tubules as assessed by endogenous lithium clearance. Treatment with ACE-I/ARB modulates proximal sodium reabsorption in the group with reabsorption that is lower than the median value for the entire study population, but not in the group with higher reabsorption. Therefore, we concluded that the effect of ACE-I/ARB treatment on sodium reabsorption in proximal tubules may be one of the antihypertensive effects of this class of drugs.

nists (ARB) has not yet been fully explained. The impact of short-term usage of ACE-I/ARB on renal sodium reabsorption has been analyzed in individual studies and has yielded variable results [5–9]. Notably, the effect of ACE-I/ARB on sodium handling was dependent on sodium intake, with a significantly stronger effect in people with lower sodium consumption; however, the intensity of the effect did not depend on the dosage of the medication [5, 6]. In previous research assessing the impact of sodium handling and concomitant left ventricular diastolic dysfunction and insulin resistance on blood pressure and arterial stiffness in individuals without diuretic treatment, the results were adjusted for antihypertensive treatment [10, 11]. In several population-based studies and observational studies including hypertensive patients, those from Central and Eastern European countries had moderate-to-high sodium intakes [12]. Currently, we set out to investigate whether long-term treatment with ACE-I or ARB and possibly other confounding factors influence sodium handling in a large group of subjects with prevailing sodium intake. To the best of our knowledge, no similar studies have been published thus far.

METHODS

Study population

In the years 2010–2015, as part of our research grants, we enrolled 490 subjects: 135 hypertensive patients followed up at a tertiary outpatient hypertension center [10], 52 obese patients awaiting bariatric surgery [13], and 303 subjects from the general population, participants of the family-based long-term observational study, with the last follow-up data collection between 2012 and 2014 [14]. The patients with a history of malignancy, decompensated long-term diseases, cardiomyopathy of unknown etiology, hemodynamically significant valvular heart disease, or secondary hypertension were excluded from the study. Based on a questionnaire, information about the type of currently used long-term antihypertensive treatment was gathered. Some of the questionnaire data, regarding patients undergoing ambulatory treatment, did not include information about the dosages of their medications; therefore, the analysis included only medication class without taking into account the dosage. To avoid interference between sodium excretion/reabsorption and the use of diuretic agents, only the participants not receiving diuretic treatment (357 subjects) were included in the study. In the morning, a fasting blood sample was obtained from each participant for biochemical serum measurements. Each participant recruited to the study completed a 24-hour urine collection to measure the 24-hour excretion of sodium ($U_{Na}V$), creatinine, and lithium. The methodology of renal sodium handling assessed by lithium clearance measurements has been previously described [10, 15].

Six patients were excluded from the statistical analysis: 2 because of failure to complete the urine collection and 4 because of high serum lithium levels (>2.0 μmol/l) and urinary lithium levels (>25.0 μmol/l) that may have indicated external contamination or high dietary lithium intake. Thus, 351 subjects were included in the statistical analysis.

Ethics

This study protocol was reviewed and approved by the Bioethical Committee of the Jagiellonian University (approval numbers: KBET/141/B/2009, KBET/155/B/2011, and KBET/57/B/2010). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants included in the study.

Statistical analysis

Database management and statistical analyses were performed using SAS System 9.3 software (SAS Institute Inc., Cary, NC, US). The distributions of the analyzed quantitative variables were compared with the normal distribution using the Shapiro-Wilk and Kolmogorov-Smirnov tests. In the descriptive statistics, the quantitative data were expressed as mean values and standard deviations (for the data with normal distribution) or as median values and interquartile ranges (for the data that did not fulfill the criteria of normal distribution). The qualitative data were expressed as proportions. To compare the mean values in the groups of patients, Student's t-test was used. Alternatively, the Wilcoxon test was used in the case of skewed distribution of quantitative variables in some subgroups. The χ^2 Pearson's test or Fisher's test were used for qualitative variables. The correlations of quantitative sodium parameters were analyzed using the standardized Spearman correlation analysis. General linear models were used to obtain the mean values of sodium parameters. Multiple linear regression analysis was performed to identify the factors associated with the analyzed sodium parameters (FPR_{Na}, FDR_{Na}, $U_{Na}V$) in the whole study group

and the subgroups with FPR_{Na}, $FDR_{Na,}$ and $U_{Na}V$ below and above the median values.

RESULTS

Characteristics of the study population

The study population involved 351 individuals, including 158 men (45.0%) and 193 women (55.0%). The mean (standard deviation) age for the whole group was 47.6 (15.6) years, body mass index (BMI) was 27.9 (7.0) kg/m^2, and the number of patients treated with ACE-I or ARB was 75 (21.4%). The estimated median value of 24-hour sodium intake, assessed on the basis of 24-hour urine collection ($U_{Na}V$) was 153.6 (113.9–200.2) mmol. The median values of fractional lithium excretion (FE_{Li}), renal sodium reabsorption in proximal (FPR_{Na}) and distal (FDR_{Na}) tubules, assessed by endogenous lithium clearance were 17.9% (12.7–25.1%,) 82.1% (74.9–87.3%), and 96.3% (94.3–97.6%), respectively.

Factors determining sodium parameters and their mutual relations

In the available literature, two markers of sodium reabsorption in proximal tubules, such as FE_{Li} and FPR_{Na} have been described, and both of them were analyzed separately to assess their mutual dependence and relationships with other parameters of lithium and sodium management. The correlation analyses were conducted in the whole group and in the subgroups identified on the basis of the median values of sodium handling parameters. As the correlation between FE_{Li} and FPR_{Na} in the whole group as well as in groups divided according to the medians reached the value of r = 1.0 (P <0.001), in subsequent analyses, the FPR_{Na} parameter was used to facilitate interpretation of results, reflecting the co-linearity between the value of FPR_{Na} and the magnitude of sodium reabsorption in the proximal tubules.

In the whole group, above and below the median value of FPR_{Na}, FPR_{Na} showed a significant negative relationship with lithium clearance (r = –0.64; P <0.001; r = –0.35; P <0.001 and r = –0.57; P <0.001), respectively. FDR_{Na} in the whole group and after division by the median showed a significant positive relation with lithium clearance (r = 0.39; P <0.001; r = 0.51; P <0.001 and r = 0.43; P <0.001), respectively. In the whole group and in the subgroups above and below the median value of FPR_{Na}, FPR_{Na} did not show a significant relation with $U_{Na}V$ (r = 0.08; P = 0.12; r = 0.12; P = 0.10 and r = 0.11; P = 0.14), respectively. FDR_{Na} showed a significant negative relation with $U_{Na}V$ in the whole group (r = –0.45; P <0.001), and the subgroups above (r = –0.31; P <0.001) and below (r = –0.32; P = 0.001) the median.

Determinants of renal sodium handling

Based on the obtained data, sodium handling parameters i.e. dietary sodium intake (reflected by $U_{Na}V$) and sodium reabsorption in renal tubules (reflected by endogenous lithium parameters, that is, FPR_{Na} and FDR_{Na}), were standardized for age, sex, BMI, hypoglycemic treatment, antihypertensive treatment with beta-blockers, calcium channel blockers, and ACE-Is/ARBs. The analyses were conducted in the whole group and the subgroups with $U_{Na}V$, $FPR_{Na,}$ and FDR_{Na} above and below the median value. Clinical, biochemical, and medication characteristics of the study group divided by FPR_{Na} are summarized in Table 1.

Table 1. Clinical characteristics of the study population, biochemical studies in serum, 24-hour urine collection, and the parameters obtained using endogenous lithium clearance, divided by FPR_{Na} median

	FPR_{Na} < median n = 176	FPR_{Na} ≥ median n = 175	*P*-value
Clinical characteristics			
Age, years	48.9 (15.5)	46.2 (15.5)	0.11
Male, n (%)	74 (42.1)	84 (48.0)	0.26
Height, cm	168.5 (9.6)	170.2 (9.0)	0.07
Weight, kg	80.5 (22.1)	79.9 (20.8)	0.80
BMI, kg/m^2	28.3 (7.2)	27.5 (6.8)	0.31
Waist, cm	94.2 (18.2)	93.7 (16.3)	0.79
Hip, cm	106.2 (13.0)	105.6 (12.9)	0.69
WHR	0.88 (0.10)	0.88 ± (0.09)	0.87
Serum and 24-hour urine parameters			
Sodium, mmol/l	139.8 (2.1)	139.9 (2.2)	0.65
Creatinine, µmol/l	72.2 (13.2)	71.9 (14.6)	0.82
Volume, ml	1615.9 (611.3)	1504.3 (579.9)	0.08
Sodium excretion, mmol	165.3 (79.1)	165.3 (64.1)	0.99
Creatinine excretion, mmol	11.5 (4.1)	15.2 (15.1)	0.002
Sodium clearance, ml/min/1.73 m^2	0.8 (0.4)	0.6 (0.3)	0.98
FE_{Na}, %	0.8 (0.3)	0.6 (0.3)	0.001
Creatinine clearance, ml//min/1.73 m^2	116.6 (32.1)	130.6 (35.9)	0.13
Endogenous lithium clearance			
Serum lithium, µmol/l	0.07 (0.2)	0.15 (0.4)	0.05
Urine lithium, µmol/l	2.1 (3.4)	1.9 (4.3)	0.66
Lithium excretion, µmol/24 h	9.1 (8.1)	7.9 (13.3)	0.30
Lithium clearance, ml/min/1.73 m^2	27.7 (20.6–40.6)	14.3 (11.2–19.3)	0.001
FE_{Li}, %	25.1 (20.7–36.9)	12.7 (9.7–15.7)	0.001
FDR_{Na}, %	97.4 (96.4–98.3)	94.7 (92.8–96.3)	0.001
FPR_{Na}, %	74.9 (63.1–79.2)	87.3 (84.3–90.3)	0.001
Antihypertensive treatment			
ACE-I, n (%)	41 (23.3)	22 (12.6)	0.008
ARB, n (%)	5 (2.8)	7 (4.0)	0.55
CCB, n (%)	27 (15.3)	15 (8.6)	0.05
BB, n (%)	41 (23.3)	30 (17.1)	0.15
Hypoglycemic treatment, n (%)	4 (2.3)	4 (2.3)	0.42

The data are presented as arithmetical means (standard deviations), percentages, or median values with interquartile ranges

Abbreviations: BB, beta-blockers; BMI, body mass index; CCB, calcium channel blockers; FDR_{Na}, fractional distal sodium reabsorption; FE_{Li}, fractional lithium excretion; FE_{Na}, fractional sodium excretion; FPR_{Na}, fractional proximal sodium reabsorption; WHR, waist-to-hip ratio

The multiple regression analyses performed in the entire population showed a strong negative association between FPR_{Na} and ACE-I/ARB treatment (b = –19.5; SE = 4.9; P <0.001), with no relationship to other parameters. When we subdivided the study group according to the median

Table 2. Determinants of renal sodium handling

Determinants	FPR_{Na}	FPR_{Na} < median	FPR_{Na} ≥ median	FDR_{Na}	$U_{Na}V$
R^2	0.007	0.1	0.1	0.05	0.02
Partial regression coefficient (SE)					
Age, years	0.05 (0.1)	0.2 (0.2)	–0.06 (0.02)[b]	0.007 (0.01)	0.2 (0.3)
Sex (male)	–4.3 (3.3)	–7.4 (6.1)	–0.1 (0.6)	1.0 (0.3)[c]	–57.0 (7.5)[c]
BMI, kg/m^2	–0.3 (0.3)	–0.8 (0.4)	0.002 (0.02)	27.7 (7.6)	1.0 (0.6)
Hypoglycemic treatment	7.4 (7.6)	7.9 (13.7)	1.3 (1.4)	–1.0 (0.7)	11.9 (17.3)
Treatment with BB	6.9 (4.7)	10.8 (7.9)	–0.9 (1.0)	0.03 (0.4)	–1.8 (10.8)
Treatment with CBB	1.1 (5.6)	7.0 (9.4)	1.4 (1.1)	–0.3 (0.5)	5.3 (12.8)
Treatment with ACE-I/ARB	–19.5 (4.9)[c]	–30.4 (8.6)[c]	0.1 (0.9)	0.4 (0.4)	1.4 (11.2)

Significance of the partial regression coefficients: [a]$P \leq 0.05$; [b]$P \leq 0.01$; [c]$P \leq 0.001$

Abbreviations: see Table 1

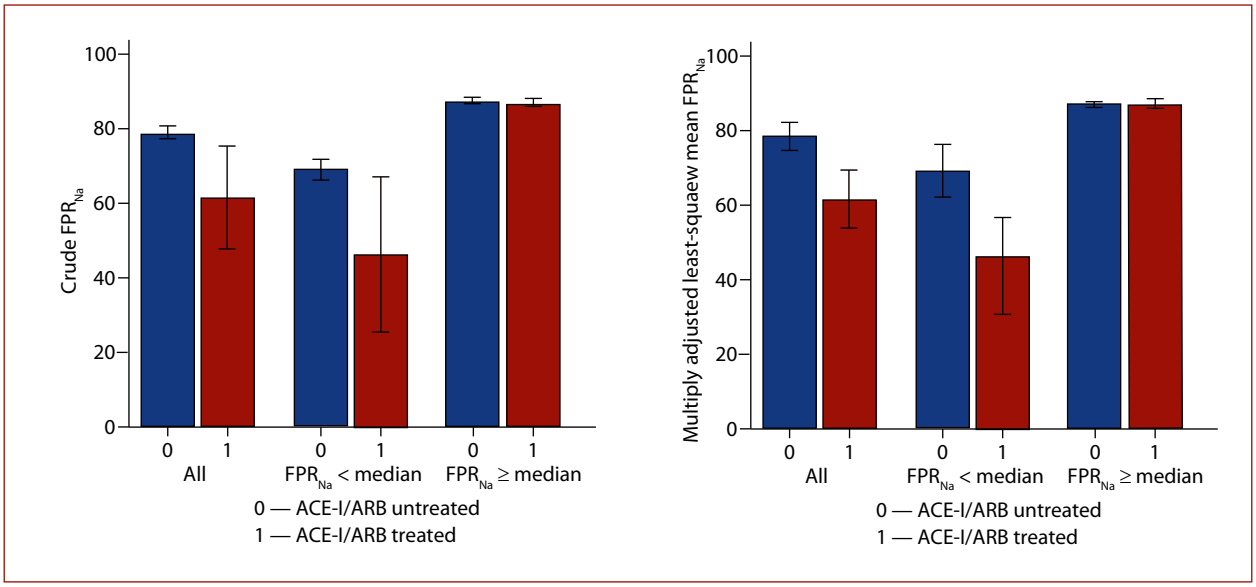

Figure 1. Associations between sodium reabsorption in proximal tubules and ACE-I/ARB treatment according to the median value of FPR_{Na}

The data are presented as arithmetic means (standard deviations)
Parameters of fractional sodium reabsorption in renal proximal tubules (FPR_{Na}) with reference to angiotensin-converting enzyme inhibitors (ACE-I)/angiotensin-II-receptor antagonists (ARB) treatment, in the whole group and in the subgroups divided by the median values of FPR_{Na}. The data in groups divided relative to ACE-I/ARB treatment were crude and standardized for age, sex, body mass index, hypoglycemic treatment, antihypertensive treatment with beta-blockers, calcium channel blockers, and ACE-Is/ARBs.

value of FPR_{Na}, individuals with higher sodium reabsorption in proximal tubules showed a significant adverse association between FPR_{Na} and age (b = –0.06; SE = 0.02; P = 0.003), with no association with ACE-I/ARB treatment (b = 0.1; SE = 0.9; P = 0.90). On the contrary, in subjects with FPR_{Na} below the median value, we found a strong significant negative relationship between FPR_{Na} and ACE-I/ARB treatment (b = –30.4; SE = 8.6; P <0.001), with no association with other parameters (Table 2). In these analyses, FPR_{Na} was significantly associated with long-term ACE-I/ARB treatment in individuals in whom sodium reabsorption in proximal tubules was lower than the median value for the entire study population. In contrast, only in these individuals whose proximal sodium reabsorption was higher than the median value, FPR_{Na} was significantly associated with age. However, that association was not apparent in the whole studied group. As statistically significant relationships were found, we conducted additional analyses using adjusted analysis of variances (ANOVA) for the whole group of subjects and in the subgroups according to median values of FPR_{Na}, with respect to ACE-I/ARB treatment (Figure 1).

Sensitivity analysis, conducted in the groups divided by sex (P <0.03 in sex groups above the median value of FPR_{Na}, and P <0.05 in sex groups below the median value of FPR_{Na}) and by the median of $U_{Na}V$, confirmed the relationship between FPR_{Na} and ACE-I/ARB treatment. In subjects with $U_{Na}V$ below the median value, a significant negative relationship between FPR_{Na} and ACE-I/ARB treatment was demonstrated (b = –31.2; SE = 9.04; P <0.001), with no association in the group with $U_{Na}V$ above the median value (b = –8.23; SE = 4.42; P = 0.08). Sensitivity analysis performed in individuals with $U_{Na}V$ above the median value did not confirm prior findings for age (b = –0.14; SE = 0.11; P = 0.23). Determinants of renal sodium handling in relation to FDR_{Na} and $U_{Na}V$ are presented in Table 2, with no relationship with ACE-I/ARB treatment.

DISCUSSION

In a large group of Caucasian subjects without diuretic treatment with prevailing sodium consumption, we demonstrated the associations between long-term treatment with ACE-I or ARB and renal sodium reabsorption in proximal tubules as assessed by endogenous lithium clearance. Treatment with ACE-I/ARB modulates FPR_{Na} in the group with lower reabsorption, but not in that with reabsorption higher than the median value for the entire study population. Sensitivity analysis, conducted in the groups divided by sex and median of daily sodium excretion confirmed the abovementioned relationships. The results of the study, therefore, allow us to assume that the effect of ACE-I/ARB treatment on sodium reabsorption in proximal tubules may be one of antihypertensive effects of this class of drugs.

The processes of sodium excretion and reabsorption undergo complex regulation. The method of a single measurement of sodium in a 24-hour urine sample was considered for many years a gold standard [16]; however, in light of the newest studies, it has been found to be susceptible to the possibility of significant measurement errors. It turned out that a single $U_{Na}V$ measurement does not reflect daily sodium intake, and the measurement error can be as high as 3.0 g NaCl/day [17], which indicates the necessity of taking multiple measurements [18] and using alternative measurement methods. One of the alternative methods of assessing sodium handling could be the technique of measuring daily endogenic lithium clearance. Studies in animal models showed that under steady-state conditions, evaluation of proximal renal sodium reabsorption can be free of measurement bias [19]. Expression of renal clearance of lithium as fractional excretion provides a measure that is factored for the glomerular filtration rate (GFR) and free of possible bias such as incomplete urine collection or difference in the urinary flow rate [20]. In clinical trials, most researchers prefer to use FE_{Li} [2–4], which represents clearance of lithium divided by the glomerular filtration rate assessed by creatinine clearance, rather than FPR_{Na} [21, 22], which is a surrogate taking into account the value of FE_{Na}.

Extensive research suggests that higher FPR_{Na} has been found in individuals with abdominal adiposity, metabolic syndrome, diabetes, or insulin resistance [2–4]. Schwotzer et al. [23] analyzed the influence of insulin resistance assessed by adipokines (leptin and adiponectin) on sodium handling parameters in a group of untreated people of African descent. They found that leptin was positively associated with $U_{Na}V$ and FPR_{Na}, and sex and obesity were the major confounders of that association. In a recently published study performed in a group of 1409 untreated participants in relation to environmental and genetic factors, both FE_{Li} and FDR_{Na} were significantly associated with season and humidity, but not with outdoor temperature or atmospheric pressure. After adjustment for host and environmental factors, among the 19 studied genetic variants, only one of them — rs12513375 was significantly associated with FE_{Li} and FDR_{Na} and accounted for 1.7 % of the variance [24].

Kidneys have many angiotensin II (Ang II) receptors, whose activation alters hemodynamics, glomerular permeability, and urinary electrolyte excretion. In animal and human models, infusion of Ang II results in a decrease of renal flow and subsequent reduction of GFR due to vasoconstriction. Moreover, Ang II directly affects the glomerulus, leading to a reduced ultrafiltration index and GFR [25, 26]. These mechanisms, together with the direct effects of Ang II on renal tubules, lead to decreased urinary sodium excretion and stimulation, first an increase in FPR_{Na} and later an increase in FDR_{Na} [26]. ACE-I have the opposite effect and tend to enhance both absolute and fractional sodium excretion [27]. Hollenberg et al. [5] demonstrated that a single dose of captopril (of 5 to 100 mg) increases renal blood flow, maintains GFR, and enhances sodium excretion. This effect was more pronounced in subjects with high activity of the renin–angiotensin–aldosterone system (which is physiological in people on a low-sodium diet), and the higher doses of ACE-I prolong the duration of the drug impact on renal function, but they do not enhance the magnitude of response to ACE-I. In the available literature, only limited studies use the lithium clearance technique to establish effects of short-term ACE-I treatment on sodium reabsorption in renal tubules. In a group of 32 patients with essential hypertension who received 2-week placebo and then 4-week open-label ACE-I treatments, GFR, renal plasma flow, and lithium clearance were measured after orally administrated lithium to establish the degree of sodium reabsorption in renal tubules. It transpired that short term ACE-I treatment significantly reduced sodium reabsorption in proximal tubules [9]. In the literature, however, no works have assessed the impact of long-term ACE-Is treatment on renal sodium reabsorption using endogenic lithium clearance. Regarding ARBs, Burnier et al. [6] performed a detailed review of the effects of single-dose of 100 mg of losartan vs. placebo on hemodynamics and renal reabsorption of sodium assessed using endogenous lithium clearance. They suggested a direct relationship between the renin–angiotensin–aldosterone activity caused by sodium consumption and the magnitude of the drug effect, mainly expressed in distal renal tubules. In a subsequent study of 10 hypertensive patients receiving 50 mg of losartan daily for 1 month, the results were different, suggesting that FPR_{Na} rather than FDR_{Na} is influenced by the treatment [8]. Similar to ACE-I, none of the studies assessed the impact of long-term treatment with ARBs on renal sodium absorption as measured by endogenic lithium clearance. In our study, performed in a group of 351 subjects with prevailing sodium consumption, we found that the long-term treatment with ACE-I/ARB strongly influences FPR_{Na} in the subgroup with lower sodium reabsorption and in the subgroup on a low sodium diet. A combined analysis of the impact of ACE-I and ARB on parameters of endogenic lithium clearance appears to be a sensible approach. Only

one study conducted on a group of 10 healthy volunteers, found that a one-time administration of 20 mg of enalapril and a subsequent administration of 50 mg of losartan did not significantly affect endogenic lithium clearance parameters [7]. Otherwise, it appears that in relation to synergistic effects of medications on pressure and hormonal parameters, their impact on lithium and sodium reabsorption is also synergistic and might only become apparent after a longer period of use.

Our results should be interpreted in the context of the strengths and limitations of this study. The presented group of 351 people is, as far as we are aware, the largest group in which analysis of factors influencing sodium management taking into account long-term ACE-I/ARB treatment as measured by endogenic lithium clearance was performed. However, this group, free from diuretic treatment, was not homogeneous — 19.9 % were recruited from patients with long-standing treated hypertension, 7.7% from patients with morbid obesity qualified for bariatric surgery, and 72.4% from the general population. The percentage of people undergoing ACE-I/ARB treatment in the study group was 21.4%. Additionally in the group recruited from the general population, comprising 42.7% of people undergoing ACE-I/ARB treatment, no information regarding the dosages of administered antihypertensive medication was gathered. The lack of this information made it impossible to assess the impact of ACE-I and ARB dosage on sodium handling parameters. Our previous studies using the endogenous lithium technique [10, 11] took into account antihypertensive treatment in the standardization. In light of the aforementioned results, it would appear, that standardization should be narrowed down to ACE-I and ARB medications, especially in populations with low or moderate sodium consumption.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Minegishi S, Luft FC, Titze J, et al. Sodium handling and interaction in numerous organs. Am J Hypertens. 2020; 33(8): 687–694, doi: 10.1093/ajh/hpaa049, indexed in Pubmed: 32198504.
2. Barbato A, Cappuccio FP, Folkerd EJ, et al. Metabolic syndrome and renal sodium handling in three ethnic groups living in England. Diabetologia. 2004; 47(1): 40–46, doi: 10.1007/s00125-003-1260-z, indexed in Pubmed: 14618235.
3. Strazzullo P, Barbato A, Galletti F, et al. Abnormalities of renal sodium handling in the metabolic syndrome. Results of the Olivetti Heart Study. J Hypertens. 2006; 24(8): 1633–1639, doi: 10.1097/01.hjh.0000239300.48130.07, indexed in Pubmed: 16877967.
4. D'Elia L, Cappuccio FP, Iacone R, et al. Altered renal sodium handling and risk of incident hypertension: Results of the Olivetti Heart Study. PLoS One. 2017; 12(2): e0171973, doi: 10.1371/journal.pone.0171973, indexed in Pubmed: 28196131.
5. Hollenberg NK, Meggs LG, Williams GH, et al. Sodium intake and renal responses to captopril in normal man and in essential hypertension. Kidney Int. 1981; 20(2): 240–245, doi: 10.1038/ki.1981.126, indexed in Pubmed: 7026873.
6. Burnier M, Rutschmann B, Nussberger J, et al. Salt-dependent renal effects of an angiotensin II antagonist in healthy subjects. Hypertension. 1993; 22(3): 339–347, doi: 10.1161/01.hyp.22.3.339, indexed in Pubmed: 8349327.
7. Schmitt F, Natov S, Martinez F, et al. Renal effects of angiotensin I-receptor blockade and angiotensin convertase inhibition in man. Clin Sci (Lond). 1996; 90(3): 205–213, doi: 10.1042/cs0900205, indexed in Pubmed: 8777826.
8. Fauvel JP, Velon S, Berra N, et al. Effects of losartan on renal function in patients with essential hypertension. J Cardiovasc Pharmacol. 1996; 28(2): 259–263, doi: 10.1097/00005344-199608000-00012, indexed in Pubmed: 8856482.
9. Semplicini A, Ceolotto G, Sartori M, et al. Regulation of glomerular filtration in essential hypertension: role of abnormal Na+ transport and atrial natriuretic peptide. J Nephrol. 2002; 15(5): 489–496, indexed in Pubmed: 12455714.
10. Cwynar M, Gąsowski J, Stompór T, et al. Blood pressure and arterial stiffness in patients with high sodium intake in relation to sodium handling and left ventricular diastolic dysfunction status. J Hum Hypertens. 2015; 29(10): 583–591, doi: 10.1038/jhh.2015.1, indexed in Pubmed: 25631217.
11. Cwynar M, Gąsowski J, Gryglewska B, et al. Insulin resistance and renal sodium handling influence arterial stiffness in hypertensive patients with prevailing sodium intake. Am J Hypertens. 2019; 32(9): 848–857, doi: 10.1093/ajh/hpz063, indexed in Pubmed: 31102435.
12. Burnier M. Controversies in the management of patients with arterial hypertension. Kardiol Pol. 2019; 77(10): 902–907, doi: 10.33963/KP.15002, indexed in Pubmed: 31571674.
13. Głuszewska A, Gryglewska B, Gąsowski J, et al. Reduction of 24-h blood pressure variability in extreme obese patients 10 days and 6 months after bariatric surgery depending on pre-existing hypertension. Eur J Intern Med. 2019; 60: 39–45, doi: 10.1016/j.ejim.2018.10.022, indexed in Pubmed: 30420135.
14. Kloch M, Stolarz-Skrzypek K, Olszanecka A, et al. Inflammatory markers and left ventricular diastolic dysfunction in a family-based population study. Kardiol Pol. 2019; 77(1): 33–39, doi: 10.5603/KP.a2018.0214, indexed in Pubmed: 30406940.
15. Chiolero A, Maillard M, Nussberger J, et al. Proximal sodium reabsorption: An independent determinant of blood pressure response to salt. Hypertension. 2000; 36(4): 631–637, doi: 10.1161/01.hyp.36.4.631, indexed in Pubmed: 11040249.
16. Luft FC, Fineberg NS, Sloan RS. Estimating dietary sodium intake in individuals receiving a randomly fluctuating intake. Hypertension. 1982; 4(6): 805–808, doi: 10.1161/01.hyp.4.6.805, indexed in Pubmed: 7141607.
17. Lerchl K, Rakova N, Dahlmann A, et al. Agreement between 24-hour salt ingestion and sodium excretion in a controlled environment. Hypertension. 2015; 66(4): 850–857, doi: 10.1161/HYPERTENSIONAHA.115.05851, indexed in Pubmed: 26259596.
18. Birukov A, Rakova N, Lerchl K, et al. Ultra-long-term human salt balance studies reveal interrelations between sodium, potassium, and chloride intake and excretion. Am J Clin Nutr. 2016; 104(1): 49–57, doi: 10.3945/ajcn.116.132951, indexed in Pubmed: 27225435.
19. Burnier M, Bochud M, Maillard M. Proximal tubular function and salt sensitivity. Curr Hypertens Rep. 2006; 8(1): 8–15, doi: 10.1007/s11906-006-0035-6, indexed in Pubmed: 16600154.
20. Strazzullo P, Galletti F, Barba G. Altered renal handling of sodium in human hypertension: short review of the evidence. Hypertension. 2003; 41(5): 1000–1005, doi: 10.1161/01.HYP.0000066844.63035.3A, indexed in Pubmed: 12668589.
21. Seidlerová J, Staessen JA, Maillard M, et al. Association between arterial properties and renal sodium handling in a general population. Hypertension. 2006; 48(4): 609–615, doi: 10.1161/01.HYP.0000240516.60040.ba, indexed in Pubmed: 16966578.
22. Jin Y, Kuznetsova T, Maillard M, et al. Independent relations of left ventricular structure with the 24-hour urinary excretion of sodium and

aldosterone. Hypertension. 2009; 54(3): 489–495, doi: 10.1161/HYPERTENSIONAHA.109.130492, indexed in Pubmed: 19581508.
23. Schwotzer N, Burnier M, Maillard M, et al. Sex and body mass index modify the association between leptin and sodium excretion: a cross-sectional study in an African population. Am J Hypertens. 2019; 32(11): 1101–1108, doi: 10.1093/ajh/hpz106, indexed in Pubmed: 31257412.
24. Kang YY, Cheng YB, Guo QH, et al. Renal sodium handling in relation to environmental and genetic factors in untreated Chinese. Am J Hypertens. 2021; 34(4): 394–403, doi: 10.1093/ajh/hpaa160, indexed in Pubmed: 33005923.
25. Rosivall L, Carmines PK, Navar LG. Effects of renal arterial angiotensin I infusion on glomerular dynamics in sodium replete dogs. Kidney Int. 1984; 26(3): 263–268, doi: 10.1038/ki.1984.168, indexed in Pubmed: 6513271.
26. Eiskjaer H, Sørensen SS, Danielsen H, et al. Glomerular and tubular antinatriuretic actions of low-dose angiotensin II infusion in man. J Hypertens. 1992; 10(9): 1033–1040, indexed in Pubmed: 1328362.
27. Hall JE, Guyton AC, Smith MJ, et al. Chronic blockade of angiotensin II formation during sodium deprivation. Am J Physiol. 1979; 237(6): F424–F432, doi: 10.1152/ajprenal.1979.237.6.F424, indexed in Pubmed: 391063.