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Original article

Role of Urinary Fractional exertion of Sodium in Resistant Hypertension Patients

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Abstract:

Background: Hypertension is recorded as a main cause of disability and death in the world. Excessive sodium ingestion is associated with elevated BP and can attribute to poor BP control despite the use of antihypertensive medications. The aim of our study was to correlate between fractional sodium excretion (as marker to daily sodium consumption) and resistant HTN. **Methods:** The current study is a single center prospective study conducted on 50 Patients complaining of 1ry type of hypertension at outpatient, inpatient cardiology ward and cardiac care unit in Nasser institute Hospital and according to control of BP, patients were divided into two groups; I: patients with controlled hypertension and Group II: patients with uncontrolled (resistant) hypertension. **Results:** There was significant higher office systolic and diastolic BP in group II ($p<0.05$). Also mean 24hr systolic and diastolic BP was higher in group II. Regarding dipping criteria; there was higher percentage of patients of group II that had non-dipping and reverse dipping BP compared to group I ($p=0.020$). There were no significant differences as regards $FENa^+$ results between the 2 groups ($P=0.093$), while 24h urinary sodium excretion came out with significant higher value in group II ($P=0.043$) and the amount of 24-hr urinary sodium shows significant correlation regarding hypertension treatment resistance ($P = 0.045$). **Conclusion:** 24h urine sodium, and so "increased dietary sodium amount", could be considered predictor for resistance to antihypertensive TTT, as we found that 24-h Na^+ kidney excretion was highly associated with both mean24-h AMBP and office BP elevation.

Key words: $FENa^+$ - Hypertension – Sodium.

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Introduction:

High BP has been recorded as a main cause of morbidity and death in both rich and poor populations. Individuals with HTN are susceptible to CVDs, stroke, or kidney failure. It is estimated that the overall prevalence of HTN in adults is > 30% **(1).**

Among reasons of HTN, salt intake is a vital lifestyle aspect. Excessive sodium intake is associated with elevated blood pressure (BP). It can attribute to poor BP control despite the use of antihypertensive medications. However, only a few short-term controlled trials with small sample size and other cross sectional have evaluated the relation between high Na^+ intake and poor BP control **(2).**

Although excessive consideration has been given on handling approaches that improve adherence to TTT schedules like self-care activities for firm BP control, majority of the pts in health care authorities received medicine but not lifestyle training, representing incomplete follow up to guidelines. For instance, only thirty percent of HTN patients practice daily life changes as a management of HTN **(3).**

Cross sectional studies measured sodium intake by dietary survey method and spot urine method known to have limitations. Moreover, they measured casual BP, not ambulatory BP which known to have stronger association with future cardiovascular events than casual BP **(2).**

In the common population, both high Na^+ and low K^+ ingestion, assessed by urine secretion analysis, associate with increased BP readings and HTN onset. The beneficial focus should be on optimizing salt depleting TTT by assessing and, decreasing dietary salt intake, maximizing diuretics, and adding a MRAs if there are no contraindications.**(4)**

The aim of our study was to correlate between $FENa^+$ level and resistant HTN.

Patients and Methods

Type of study

- Case control prospective study.

Period of study:

- 2 years.

Sample setting:

- Outpatient clinic, inpatient cardiology ward and cardiac care unit in Nasser institute Hospital.

Study design:

The study was planned as a single center prospective study on 50 patients who suffered from 1ry HTN among those attending to outpatient clinic, inpatient cardiology ward and cardiac care unit in Nasser institute Hospital from 4-2021 to 3-2023.

Inclusion criteria

- 25 controlled HTN patients [24 hour (mean BP) ≥130 ≥80 mmHg] (control group).

• 25 patients with diagnosis of resistant 1ry type of hypertension on regular treatment and frequent visits to hospital had enrolled in this study.

Exclusion criteria

• Secondary causes of HTN as:
✓Renal disease, Patients on hemodialysis, renal artery stenosis, renal segmental hypoplasia.
✓Endocrinal disorders, Pheochromocytoma, Hyperaldosteronism, Thyroid diseases, Cushing syndrome, Acromegaly.
✓Pregnancy induced HTN.
✓Cancer patients.
✓Co-arctation of aorta.
✓ Immunological diseases.
✓Chronic liver disease.
✓Symptomatic heart failure.
✓Pre-renal azotemia, acute glomerulonephritis, ATN or sepsis.

For all patients:

▪ Informed consent.
▪ Demographic data:

-Age

-Sex

▪ Careful history taking:

-Family history of HTN.

-Treatment of HTN and doses.

-Other CV risk factors: smoking, DM.

▪12 lead surface ECG.
▪Labs with special concern to:

-CBC.

-Random Blood glucose level.

-Kidney function tests (serum creatinine, urea, Na^+, K^+)

-Liver function tests.

-Urine creatinine, urine Na^+, Fractional excretion of sodium ($FENa^+$).

▪ Office blood pressure measurement: Using manual sphygmomanometer.
▪ Ambulatory blood pressure measurement: Performed at thirty minute breaks at day and at sixty minute breaks at night.

Resting Trans-Thoracic Echo:

Echocardiography was performed using a vivid 5 n pro machine (GE Vingmed Ultrasound, Horten, Norway) using 3S probe in the basic parasternal and apical windows in the left side lateral status. Two-dimensional echocardiography and Doppler studies were performed for every patient.

We measured Left Ventricle (LVEDD, LVESD) from the parasternal long-axis window, estimated M-mode LV EF, and LV mass index and relative wall thickness. In addition, we measured the largest antero-posterior LA diameter at end-systole, and aortic dimension and measured the mitral inflow Doppler parameters.**(5)**

Pulsed-wave Doppler: Mitral valve stream velocity was gained from the apical view with the sample indicator placed just below the mitral tips. The following measurements were evaluated: mitral stream velocity in early diastole (Peak E),

peak mitral stream velocity in late diastole (Peak A), E/A ratio.

Tissue Doppler study (TDI): was performed in the apical 4-chamber window, with the mitral annulus perpendicular to the ultrasound ray. Pulsed TDI cursor was placed on the lateral side of the mitral annulus. Care was taken to decrease blare signals. Measurements were made of peak early diastolic (Ea), late peak diastolic myocardial velocities (Aa), peak systolic (Sa), Ea/Aa ratio and E/e' ratio at the mitral annulus.

Office BP measurement:

Using manual mercury sphygmomanometers - OMRON, Omron Health Care; According to the recommendations of European Society of hypertension; Patients were settled comfortably in a silent surroundings for 5 minutes before starting blood pressure measurements, 3 BP readings were documented (1–2 min interval), and BP was taken as the average of all.

The cuff fixed opposite to the heart, with the back and arm of the patient well supported. When using auscaltatory methods; first and fifth Korotkoff sounds were used to identify systolic and diastolic phases of BP, respectively.

Blood pressure had been measured in both arms to discover any differences between two arms and the side with the higher reading was used as the reference.**(6)**

Ambulatory BP measurement:

Performed by CONTEC medical systems ABPM 50, the device was calibrated to obtain BP measurements at thirty minute intervals at day (8 am to 12 am) and at sixty minute intervals at night (12 am to 8 am).

The mean BP readings has taken and considered HTN according to European guide lines:

Day-time (when active) ≥135 ≥85 mmHg

Night-time (when at bed) ≥120 ≥70 mmHg

24 hour (mean) ≥130 ≥80 mmHg.**(7)**

Fractional excretion of sodium ($FENa^+$):

Twenty-four hours urine collection began when the patient discarded the 1st discharged urine early morning in metered container till the 1st urination of the next day in an attempt to decrease variability of sodium levels between the different timings of urine sample collection and calculated as follow:**(8)**

$$\text{FENa} = \frac{\textbf{Urine Sodium x plasma creatinine}}{\textbf{plasma sodium x urine creatinine}} \boldsymbol{x100}$$

Ethical Approval:

Before beginning the study, it was accepted from the Ethics Committee. An official agreement was taken from every pt. This study was designed to match with the Code of Ethics of the National Association Ethical Approval (Announcement of Helsinki) for

researches including human being. {MS:24.12.2021}

Statistical methods:

Data administration and statistical examination were prepared using SPSS version 25. (IBM, Armonk,US). Quantitative data were calculated for normality using Kolmogorov–Smirnov test and direct data imagining methods. Numerical data were showed as means and SD. Categorical data were summarized as numbers and percentages. Quantitative data were compared between study groups using independent t-test. Categorical data were processed using the Chi-square or Fisher‘s exact test. Area under curve with 95% confidence interval, best cutoff point, and diagnostic indices were calculated for each. P values less than 0.05 considered significant **(9).**

Results:

There was no significant statistical difference between the 2 groups as regarding age (57.44 ± 8.63 vs. 54.76 ± 8.05 years, P value = 0.262) & gender (P value = 0.152) . Group I included 17 males (68%)& 8 females (32%). Group II included 12 males (48%) & 13 females (52%).

No differences were observed between the 2 groups as regard to the risk factors. History of DM was present in 10 patients "40%" of group I vs. sixteen patients "64%" of group II (P value = 0.089). 11 patients "44%"of group I were smokers vs. 8 patients "32%"of group II (P value = 0.382). 14 patients "56%" of group I had family history of HTN vs. 20 patients "80%" of group II (P value =0.069) the 50 patients enrolled during the study period; Their mean age was 56.10±8.37 years (range: 47-74). 29 patients (58%) were male & 21 patients (42%) were female. 26 patients (52%) were diabetic, 19 patients (38%) were smoker and 34 patients (68%) had family history of hypertension. **Table (1)**

Regarding Blood pressure measurements Patients of group II had higher mean office systolic and diastolic BP { 160.20 ± 10.46 vs. 146.32 ± 9.86 & 96.28 ± 7.59 vs. 89.76 ± 7.46; respectively (p value <0.05)}, also patients of group II had higher mean 24hr systolic and diastolic BP {143.88 ± 9.01 vs. 119.84 ± 7.56 & 90.80 ± 7.81 vs. 73.60 ± 4.78; respectively (p value <0.05)}.**(Table 2)**

Regarding dipping criteria; there was higher percentage of patients of group II that had non-dipping and reverse dipping BP compared to group I {17 (68.0%) vs. 10 (40.0%) & 8 (32.0%) vs. 7 (28.0%); respectively}. No patients in group II had either dipping or extreme dipping BP while 6 patients (24.0%) had dipping BP and 2 patients (8.0%) had extreme dipping BP in group I (p value = 0.020). **(Table 2)**

Regarding Echocardiography parameters showed statistically significant difference between two groups regarding left ventricular diastolic dysfunction 11 patients (44.0%) in group I compared to 19 patients (76.0%) in group II (P = 0.021) and the significance increased when assessed with Tissue Doppler as 11 patients (44.0%) in group I had DD compared to 21 patients (84.0%) in group

II (P = 0.003), revealing the importance of tissue Doppler when assessing diastolic function of LV as TDI is more sensitive than traditional Doppler.**(Table 3)**

Regarding Urinary Na^+ excretion findings There was no significant differences as regard to $FENa^+$ results between the 2 groups ; mean value{1.46 ± 0.40% (range: 0.93 – .25) vs. 1.76 ± 0.77% (range : 0.53 3.31)(p=0.093)} : while 24h urinary sodium excretion came out with significant higher mean value in group II than group I{141.88 ± 48.88 mmoL/L (range: 85 - 234) vs. 119.07 ± 24.94 mmoL/L (range: 88 - 182.4) (P = 0.043)}.**(Table 4)**

The amount of 24-hr urinary sodium shows significant correlation regarding hypertension treatment resistance as 4 patients (16%) of group II with Na excretion ≥ 200mmol/L showed RHT, vs 0% in group I(P=0.045).**(Table 5)**

Table (1): Patients' demographic characteristics

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		Group I	Group II	Test value	P-value	Sig.
		No. = 25	**No. = 25**			
Gender	Female	8 (32.0%)	13 (52.0%)	2.053*	0.152	NS
	Male	17 (68.0%)	12 (48.0%)			
Age per year	Mean ± SD	57.44± 8.63	54.76 ± 8.05	1.135•	0.262	NS
	Range	47 – 74	47 – 72			
HTN Family H	No	11 (44.0%)	5 (20.0%)	3.309*	0.069	NS
	Yes	14 (56.0%)	20 (80.0%)			
DM	No	15 (60.0%)	9 (36.0%)	2.885*	0.089	NS
	Yes	10 (40.0%)	16 (64.0%)			
Smoking	No	14 (56.0%)	17 (68.0%)	0.764*	0.382	NS
	Yes	11 (44.0%)	8 (32.0%)			

Table (2): Blood pressure findings among 2 groups.

		Group I No. = 25	Group II No. = 25	Test value	P-value	Sig.
Office Systolic BP (mmHg)	Mean ± SD	146.32 ± 9.86	160.20 ± 10.46	-4.829•	0.000	HS
	Range	125 – 165	130 – 170			
Office Diastolic BP (mmHg)	Mean ± SD	89.76 ± 7.46	96.28 ± 7.59	-3.062•	0.004	HS
	Range	77 – 100	77 – 110			
Mean 24H SBP	Mean ± SD	119.84 ± 7.56	143.88 ± 9.01	-10.220•	0.000	HS
	Range	103 – 129	129 – 167			
Mean 24H DBP	Mean ± SD	73.60 ± 4.78	90.80 ± 7.81	-9.393•	0.000	HS
	Range	65 – 80	72 – 105			
Dipping	Non dipping	10 (40.0%)	17 (68.0%)	9.881*	0.020	S
	Reverse	7 (28.0%)	8 (32.0%)			
	Dipping	6 (24.0%)	0 (0.0%)			
	Extreme dipping	2 (8.0%)	0 (0.0%)			

Table (3): Echocardiographic differences between both groups.

		Group I No. = 25	Group II No. = 25	Test value	P-value	Sig.
DD TDI	No	14 (56.0%)	4 (16.0%)	8.681*	0.003	HS
	Yes	11 (44.0%)	21 (84.0%)			
DD DOPPLER	No	14 (56.0%)	6 (24.0%)	5.333*	0.021	S
	Yes	11 (44.0%)	19 (76.0%)			
LVEF (%)	Mean ± SD	60.80 ± 6.18	62.64 ± 5.23	-1.136•	0.262	NS
	Range	54 – 76	54 – 71			

Table (4): Sodium excretion data in study groups.

		Group I No. = 25	Group II No. = 25	Test value	P-value	Sig.
FENa$^+$ (%)	Mean ± SD	1.46 ± 0.40	1.76 ± 0.77	-1.713•	0.093	NS
	Range	0.93 – 2.25	0.53 – 3.31			
	<1	2 (8.0%)	2 (8.0%)	1.022*	0.600	NS
	(1-3)	23 (92.0%)	22 (88.0%)			
	>3	0 (0.0%)	1 (4.0%)			
Urinary Na$^+$ (mmoL/L)	Mean ± SD	119.07 ± 24.94	141.88 ± 48.88	-2.078•	0.043	S
	Range	88 – 182.4	85 – 234			
	<100	4 (16.0%)	7 (28.0%)	6.218*	0.045	S
	100-<200	21 (84.0%)	14 (56.0%)			
	>= 200	0 (0.0%)	4 (16.0%)			

Table (5): Relation of urinary sodium level with DD and BP dipping.

		Urinary Na (mmoL/L)			Test value	P-value	Sig.
		<100	**100-<200**	**>= 200**			
		No. = 11	**No. = 35**	**No. = 4**			
HTN	Controlled	4 (36.4%)	21 (60.0%)	0 (0.0%)	6.218*	0.045	S
	Uncontrolled	7 (63.6%)	14 (40.0%)	4 (100.0%)			
DD TDI	No	2 (18.2%)	15 (42.9%)	1 (25.0%)	2.440*	0.295	NS
	Yes	9 (81.8%)	20 (57.1%)	3 (75.0%)			
DD DOPPLER	No	2 (18.2%)	17 (48.6%)	1 (25.0%)	3.628*	0.163	NS
	Yes	9 (81.8%)	18 (51.4%)	3 (75.0%)			
Dipping	Non dipping	3 (27.3%)	20 (57.1%)	4 (100.0%)	8.407*	0.210	NS
	Reverse	6 (54.5%)	9 (25.7%)	0 (0.0%)			
	Dipping	2 (18.2%)	4 (11.4%)	0 (0.0%)			
	Extreme dipping	0 (0.0%)	2 (5.7%)	0 (0.0%)			

Discussion

In the present study there was significant higher office systolic and diastolic BP measurements in uncontrolled group ($p<0.05$). Also mean 24hr systolic and diastolic BP was higher in uncontrolled group.

Regarding dipping criteria in our results; there was higher percentage of patients with uncontrolled HTN (group II) that had non-dipping and reverse dipping BP compared to group I ($p=0.020$) and no patient had either dipping or extreme dipping BP in same

group.

In concordance to our results another study found that pts with MUCH had significantly increased systolic & diastolic office BP and higher 24 hr mean SBP & DBP compared to those in the controlled hypertension group **(10).**

Similar to current study previous study showed that patients with MUCH had higher office and ambulatory systolic and diastolic BP values (p value < 0.001). Also higher BP dipping rate (either systolic or diastolic) was more prevalent in controlled vs. uncontrolled HTN groups **(11).**

Consistent to the present study another study found systolic BP, diastolic BP and Pulse pressure were considerably higher in uncontrolled HTN compared to the controlled HTN group, (p<0.001). Also, pulse pressure in uncontrolled HTN patients was higher than their normotensive peers (p <0.001) **(12).**

Also, consistent to our results, other group who evaluated the association between Na^+ ingestion and BP measurement in HTN patients. They found 24hour SBP and DBP of UTHT and UCHT groups were considerably higher than those of NT and CHT groups (P < 0.05) **(2).**

Regarding laboratory results in the present study we found that Serum creatinine was significantly higher in group I (controlled HTN) than group II (P=0.012). Also, urine creatinine was significantly higher in group I than group II (P=0.003).

While no significant differences were reported regarding serum sodium (Na+) (P=0.208), Serum potassium (K+) (P=0.696), and Serum hemoglobin (P=0.054).

In concordance to our results other studies in 2019 and 2021revealed non-significant difference between controlled and uncontrolled patients regarding serum Na& K and serum hemoglobin **(2)&(10).**

However, another research found no significant differences in blood creatinine level in MUCH against real CHTN persons **(13).**

In the current study, there were higher incidence of diastolic dysfunction either assessed by pulsed Doppler or by Tissue Doppler in uncontrolled HTN group (p<0.05) but no important difference between 2 groups in regard to LVEF (P=0.262).

In concordance to our results previous study showed no significant difference between two groups regarding LVEF (P=0.514) **(10).**

In our study there was no significant differences as regard to $FENa^+$ results between the 2 studied groups (P=0.093), while 24h urinary sodium excretion came out with significant higher value in uncontrolled BP group (P=0.043) and the amount of 24-hr urinary sodium shows significant correlation regarding hypertension treatment resistance (P = 0.045).

In our results there was significant difference between the 2 groups as regard number of patients with 24hr urinary sodium excretion >200 mmol/L (P=0.037).

Consistent to our findings, a study in 2019 who studied the dose–response relationship between 24-hour AMBP with 24-hr urine Na^+ and K^+. They found that the 24hr urine Na^+ showed an important association in a non-linear fashion with day time systolic BP

and 24hr systolic BP in all persons. Also showed an important relationship in a non-linear fashion between daytime systolic BP (P=0.0001), 24-hr systolic BP (P<0.0001), and daytime diastolic BP in the elder group **(14).**

Concordant to our results other study found that uncontrolled HTN group had the highest level of 24-hr urine Na^+. Multivariate analysis adjusted with gender, age, estimated glomerular filtration rate, body mass index, and diuretics use revealed higher level of 24-hr urine Na^+ in uncontrolled group than that in controlled one. Regression analysis revealed independent association of the amount of 24-hr urine Na^+ with uncontrolled BP in HTN patients on antihypertensive TTT **(2).**

Higher level of 24-hr kidney Na^+ secretion in uncontrolled HTN patients proved that excessive sodium ingestion could be associated with reduced BP lowering efficiency of antihypertensive drugs.

Another study group who studied the association of spot urine to creatinine ratio with single office BP reading revealed that the chief conclusion of their study was that urinary Na^+, but not K^+, was positively associated with mean arterial, pulse pressures and systolic pressure in patients with more than mild chronic kidney disease **(4).**

Also other working group found a J-arc relation between blood pressure and Na^+ ingestion, with a lowest point at 2-3 g/ d (90–130 mmol/d). In their study, the effect size of the link of systolic and diastolic BP with increasing Na^+ excretion (per 1 g/d increment) was weak in normotensive people (0.58 mm Hg for DBP and 1.30 mm Hg for SBP). It was rather greater, but still quite small, in those with HTN (0.91 mm Hg for DBP and 2.49 mm Hg for SBP) **(15).**

Again the INTERSALT study revealed an important relation between high urine Na^+ and systolic BP with increased BP deviation in middle-aged group compared to younger adults **(16).**

The PURE study, the biggest people-based study, revealed a considerable dose dependent relationship of blood pressure with 24-hr urine Na^+, K^+ and the sodium to potassium ratio. In a study by Liechtenstein and Switzerland, there was a important association between 24-hr systolic BP and urine Na^+ excretion **(15)&(17).**

Discordant to our results another study found that there was no dissimilarity between groups in 24-hr urinary Na^+, volume, or Na^+/K^+ ratio, these discordance may because patients taking drugs that affect aldosterone altitudes, such as MRAs and epithelial Na^+ channel blockers, were omitted from their research **(13).**

Conclusion:

Urinary Na^+ excretion, and so increased Na^+ oral ingestion, could be considered predictor for resistance to antihypertensive TTT, as we found that 24-hour kidney Na^+ excretion was significantly associated with both office BP readings and 24-h AMBP mean value elevation in uncontrolled group (group II) than in controlled group (group I).

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