

# Resistant Blood Hypertension and its Relationship to Sodium and Potassium Ingestion

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**Abstract—** Background: The relationship between resistant hypertension (HAR) and sodium remains controversial. This study aimed to evaluate the relationship between resistant hypertension and urinary sodium and potassium excretion. Methods: It is a cross-sectional study. Socio-demographic, clinical and laboratory variables were evaluated. The estimated consumption of Na<sup>+</sup> and K<sup>+</sup> in 24 hours was determined by the formula of Kawasaki & Tanaka (2002) and defined as high for Na<sup>+</sup> > 4g, and potassium > 4.2g. Results: Fifty-one patients with HAR were evaluated. Sodium intake increased by 56% and was associated with HAR in patients with: age between 40 and 65 years (OR = 14.91, 95% CI 1.37-162.07); Potassium intake > 4.2g (OR = 8.27; 95% CI: 1.12- 2061.16) and Caucasians (OR = 23.17; 95% CI 1.23-147.85). High potassium intake was negatively associated with uncontrolled HAR, and this association was at the threshold of statistical significance for patients with daily sodium intake of less than 4 g (OR = 0.05, 95% CI 0.01 - 1.00). Conclusion: It was observed an association between adequate blood pressure control and HAR and uncontrolled with high potassium excretion and low sodium in patients with lower age and Caucasians. The result of the present study suggests a distinct relationship of sodium and potassium among patients with resistant and uncontrolled hypertension, observed in studies investigating this association with systemic arterial hypertension.

**Index Terms** potassium, sodium, resistant hypertension, uncontrolled hypertension.

## I. INTRODUCTION

Hypertension is considered an important public health problem, affecting 30% of the adult population and approximately 1.2 billion individuals worldwide [1]. Many hypertensive individuals have high blood pressure levels, despite the use of antihypertensive medications at their most effective and tolerated pharmacological doses, or when controlled with the use of 4 or more medications, characterizing Resistant Hypertension (RH) [2].

In this scenario, the persistence of high blood pressure levels becomes relevant in public health, mainly because patients with RH are more susceptible to developing

morbidity and mortality due to cardiovascular diseases, such as stroke, acute myocardial infarction, congestive heart failure (CHF), and chronic kidney disease (CKD) when compared to individuals with controlled hypertension [3] - [5].

Although the exact prevalence of RH is not established, it is estimated that this condition affects 12 to 15% [2], and even 20-30% in hypertensive patients [6], depending on the criteria used and the geographical region. Through an 18-month cohort study with hypertensive patients who started treatment (n = 205,750 patients), it was possible to identify an incidence of 1.9% of HR [7].

The use of non-pharmacological approaches is of great importance in the treatment of hypertension. Among these, it is worth mentioning the reduction of salt in the diet. Studies in hypertensive population showed a strong relationship between diet with high salt content, and the severity of hypertension. The PURE [1] study showed that patients with high urinary sodium excretion associated with low potassium excretion had higher blood pressure levels, inversely to those with increased potassium excretion and low sodium excretion, who exhibited lower levels of blood pressure, both systolic and diastolic [1].

The controversy remains as to which daily intake of sodium is healthier and provides more protection against cardiovascular disease (CVD), although the World Health Organization (WHO) recommends a sodium intake of less than 2 g/day [8]. The aim of this study is to evaluate the relationship between resistant hypertension and sodium and potassium intake.

## II. MATERIALS AND METHODS

This was a cross-sectional study, conducted with adult patients consecutively selected from a cohort of resistant hypertension, assessed from 2014 to 2017, who used two antihypertensive medications of different classes plus a diuretic in their most effective and tolerated pharmacological doses, or controlled blood pressure with four or more drugs. Patients who were not regularly monitored at the outpatient clinic or who did not undergo the recommended laboratory evaluation for the biochemical and urinary determination of sodium, potassium and creatinine levels were excluded. Clinical interview was conducted and data were collected in medical records, and a research form was applied (demographic, clinical and laboratory data). Morisky's questionnaire<sup>9</sup> was also used to evaluate therapeutic adherence. Ambulatory Blood Pressure Monitoring (ABPM) was performed in all patients to discard pseudoresistance due to white-coat effect. All patients underwent urinary laboratory determination (urine, creatinine, sodium, microalbuminuria) and plasma (hemogram, HSV, fasting and postprandial glycemia, glycosylated hemoglobin, urea, creatinine,

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sodium, potassium, total cholesterol / HDL, LDL, triglycerides, uric acid, CRP-as).

The estimated daily intake of sodium and potassium was obtained from Kawasaki et al. (1993) [10] equation, modified by Tanaka [11] (Figure 1), who reported a model to estimate 24-hour intake by measuring these ions and urinary creatinine levels, and the relationship between them, performed in an isolated sample of morning urine, using values measured as substitutes for the determination of Na and K intake in the 24 hours [10], an equation that can be used for both sexes, validated in later studies, even in individuals taking antihypertensive medication [8].

Figure 1. Stages for calculating the estimated daily intake of sodium and potassium, from Kawasaki equation, modified by Tanaka.

(1) $PRCr \text{ (mg/dia)} = - 2.04 \times \text{idade (anos)} + 14.89 \times \text{peso (kg)} + 16.14 \times \text{altura (cm)} - 2244.45$
(2) $XNa \text{ (or XK)} = SUNa \text{ (or SUK)} / SUCr \times PRCr$
(3) $\text{Estimated do 24HUNaV (mEq/day)} = 21.98 \times XNa^{0.392}$
(4) $\text{Estimated 24HUKV (mEq/day)} = 7.59 \times XK^{0.431}$

*PRCr = 24-hour predictive creatinine value; SUCr= urinary creatinine. SUNa = Na concentration in the spot voiding urine.  
SUK = K concentration in the spot voiding urine ; 24HUNaV = 24-h urinary sodium excretion  
24HUKV = 24-h urinary potassium excretion.*

The choice of sodium and potassium intake from the values obtained from urinary excretion considered that in normal patients, more than 95% of ingested sodium is excreted in the urine, and that dietary assessment presents many operational problems, the reason why, the 24-hour urinary excretion has been used as a marker of daily sodium consumption [12]. A 24-hour urinary excretion of 4.0 grams or more was used as the cutoff point for high sodium intake, based on data from a recently published study, which showed that high sodium intake ( $\geq 4, 0 \text{ g}$ ) is associated with an increased risk of cardiovascular events and death in hypertensive populations [13].

In addition, a Brazilian study showed that in none of the Brazilian regions, household sodium availability was less than 4 g / day, or its correspondence in 10 g sodium chloride / day [14]. Regarding the estimated daily potassium intake, it was agreed to use the measurement of the tertile (<1<sup>st</sup> tertile and > 1<sup>st</sup> tertile). The 1st tertile being equivalent to 4.2 g / day (107.7 mmol / day).

The project was approved by the Ethics and Research Committee of Hospital Ana Nery under the number 138,371 on 05/11/2012. All patients signed the Informed Consent Form. The analysis procedures included univariate and bivariate descriptive analysis, stratified analysis and logistic regression. Associations were estimated using Odds Ratio (OR), and statistical inferences were based on 95% confidence intervals (95% CI).

The dependent variable was RH. Estimated daily sodium intake was the main independent variable, with a consumption  $\geq 173 \text{ mmol}$  (equivalent to 4 g of sodium / day) being adopted as exposure definition criteria. The comparison of means between groups was done by the Student's t-test for independent samples. Potential effect modifying variables were those that, in the stratified analysis, potentiated the main association and indicated heterogeneity of the effect through the homogeneity test using the Mantel Haenszel method ( $\alpha = 0.05$ ) [15]. And as potential confounders variables of the association between uncontrolled resistant hypertension and sodium intake, those

that, in addition to being simultaneously associated with exposure and outcome, do not belong to the causal pathway under investigation [15] and that determined deviations of the association measure for PR adjusted by 10% or more in relation to the gross PR. Thus, in the stratified analysis, potential confounders and effect modifiers to be included in the modeling were selected. Convenience sample size was defined in 50 patients.

The strategy of backward modeling was used in the logistic regression analysis, considering as confounders the variables that, when removed from the model, caused a difference in the one-off measures of associations  $\geq 10\%$ . The likelihood ratio test was used as a criterion to evaluate interaction ( $\alpha = 0.05$ ) [15]. The model was also diagnosed using the goodness of fit test and Pearson's residual calculation. SPSS (version 20.0) was used for the analyzes.

III. RESULTS

During the period from September 2014 to January 2017, 51 patients with RH were evaluated. The mean age was 64.3 years (SD = 10.1), with a predominance of females (57%), between 40 and 65 years old (54.9%), obese (49%), and daily intake of potassium above 4.2 grams (64.7%), sodium intake greater than or equal to 4.0 grams (57%), creatinine clearance > 89 ml / min / 1.73m<sup>2</sup> (86%), blood glucose >100 mg / dl (65.2%), total cholesterol <200 mg / dl (82.2%) and with triglycerides <150 mg / dl (68.2%) (Table 1).

**Table 1 - Sociodemographic characteristics in 51 patients, related to the health of patients treated in the outpatient clinic of severe hypertensive cardiovascular disease.**

Characteristics	N	(%)
Sex		
Male	22	43,1
Female	29	56,9
Age*		
40 to 65	28	54,9
> 65	23	45,1
Obesity (BMI)		
$\geq 30$	25	49,0
Estimated daily potassium intake***		
$\leq 4,2$ (1st tertile)	18	35,3
> 4,2 (2nd and 3rd tertile)	33	64,7
Estimated daily sodium intake***		
< 4,0	22	43,1
$\geq 4,0$	29	56,9
Blood glucose ***		
> 100	30	65,2
Total Cholesterol ****		
$\geq 200$	8	17,8
Triglycerides****		
$\geq 150$	14	31,8
Medium Creatinine (SD)		1,02 (0,26)
Creatinine clearance*****		
Absence of kidney injury (> 89)	31	86,1
Mild Renal Insufficiency (60 a 89)	5	13,9

\*years; \*\* kg/m<sup>2</sup>; \*\*\* grams; \*\*\*\*mg/dl;\*\*\*\*\* ml/min/1,73m<sup>2</sup>, Equation used in CKD-EPI -  $GFR \text{ (ml/min/1,73 m}^2) = 141 \times \text{min} \text{ (Cr/k)}^a \times \text{max} \text{ (Cr/k,1)} \times 1,209 \times 0,993^{a/84} \times 1,018 \text{ [Woman]} \times 1,159 \text{ [African american]}$  Where: GRF: Glomerular Filtration Rate; Cr: Serum Creatinine; a : - 0,329

for women and - 0,411 for men; min: minimum of serum creatinine or 1; max: maximum of serum creatinine or 1.

The prevalence of resistant and uncontrolled hypertension in the studied population was 76.5% and daily consumption of sodium estimated from 24-hour urinary excretion was high (56.9%). The prevalence of resistant and uncontrolled hypertension was higher in patients who presented higher daily sodium intake (85.7%) than the one observed in the group with the lowest intake (65.8%), but this difference was not statistically significant. No significant differences were found in the prevalence of the different stages of blood pressure (BP), according to estimated daily sodium intake. Regarding systolic pressure, blood pressure levels <130 mmHg were more frequent in subjects with a lower sodium intake, while a tendency for higher prevalences of blood pressure levels  $\geq$ 130 mmHg occurred in the highest ingestion group (p = 0.65). As for diastolic pressure, no trend was observed to increase the prevalence of higher pressure levels with a higher sodium intake (Table 2).

**Table 2** - Prevalence of resistant and uncontrolled hypertension and stages of blood pressure according to daily sodium intake in patients with RH in the outpatient of severe hypertensive cardiovascular disease.

Variable	N	(%)	Daily sodium intake		P value
			< 4,0 g* n=22 (43,1%) %	$\geq$ 4,0 g* n= 29 (56,9%) %	
Resistant and uncontrolled Hypertension	39	76,5	65,8	85,7	0,12
Systolic Blood Pressure (mm/hg)					
< 130	12	23,5	31,8	17,2	
130 to 139	10	19,6	13,6	24,1	
140 to159	15	29,4	27,3	31,0	
> 160	14	27,5	27,3	27,6	0,65
Dyastolic Blood Pressure (mm/hg)					
< 85	26	51,0	50,0	53,6	
85 to 89	7	13,7	13,6	14,3	
90 to 99	6	11,8	9,1	14,3	
$\geq$ 100	11	21,6	27,3	17,9	0,93

\*g =grams

It was observed that patients with higher sodium intake differed significantly from those with lower sodium intake, only in relation to potassium intake. It should be emphasized that, among the variables investigated, gender, age, body mass index, creatinine levels also presented expressive percentage differences between the groups. The group of patients with higher sodium intake was composed of a higher proportion of females (62% compared to the group of patients with lower sodium intake (50%), of individuals aged over 65 years (54.5%) in relation to the group with lowest sodium intake (37.9%), with BMI above 25 kg / m<sup>2</sup>, with potassium intake below the first tertile (79.3%) when compared to the group with the lowest intake (45%). It was also observed that the means of systolic and diastolic pressures in the group of patients with higher sodium intake did not differ significantly from those observed in the group with lower sodium intake (Table 3).

**Table 3** - Characteristics of the study population according to the categories of sodium intake in patients with RH in an outpatient clinic of hypertensive cardiovascular disease.

Characteristics	N	Daily Sodium Intake		P value
		<4,0 g* n=22 (43,1%) %	$\geq$ 4,0 g* n= 29 (56,9%) %	
Sex				
Male	22	50,0	37,9	
Female	29	50,0	62,1	0,41
Age (years)				
40 to 65	28	62,1	45,5	
> 65	23	37,9	54,5	0,24
Body Mass Index (kg/m <sup>2</sup> )*				
< 25	10	27,3	13,8	
25 – 29.9	16	22,7	37,9	
$\geq$ 30	25	50,0	48,3	0,39
Estimated daily potassium intake(grams)				
$\leq$ 4,2 (1st tertile)	18	45,5	79,3	
> 4,2 (2nd and 3rd tertile)	33	54,5	20,7	0,01
Creatinine Clearance**				
$\leq$ 89 (Insuf. renal leve)	5	18,2	7,1	
> 89 (Absence of kidney injury)	31	82,8	92,9	0,35
Blood Glucose (mg/dl)				
$\leq$ 100	16	38,1	32,0	
> 100	30	61,9	68,0	0,76
Total Cholesterol (mg/dl)				
< 200	37	75,0	88,0	
$\geq$ 200	8	25,0	12,0	0,26
Triglycerides (mg/dl)				
< 150	30	70,0	66,7	
$\geq$ 150	14	30,0	33,3	0,81
<u>SBP (mmHg) (average/dp)</u>		143,09 (28,94)	145,52 (37,52)	0,80
<u>DBP (mmHg) (average/dp)</u>		87,27 (13,76)	85,69 (16,12)	0,72

\*g =grams \*\* ml/min/1,73m<sup>2</sup>, equation used in CKD-EPI – GFR (ml/min/1,73 m<sup>2</sup>)=141 x min (Cr/k.)<sup>α</sup> x max (Cr/k.)1,209 x 0,993<sup>485c</sup> x 1,018 [Woman] x 1,159 [African american] Where: GFR: Glomerular Filtration Rate; Cr: Serum Creatinine; α : - 0,329 for women and - 0,411 for men; min: minimum of serum creatinine or 1; max: maximum of serum creatinine or 1

In the stratified analysis results, the covariates potassium intake, age and ethnicity were identified as potentially modifying the effect of the association between higher sodium intake and the presence of resistant hypertension. It was found that higher sodium intake was significantly associated with resistant hypertension only in the group of patients with higher potassium intake (OR = 8.27; 95% CI: 1.12 - 61.16), even after adjusting for creatinine urinary and BMI. It was found that in patients between 40 and 65 years old, resistant and uncontrolled hypertension was significantly associated with higher sodium intake (OR = 14.91, 95% CI, 1.37-162.07). On the other hand, among patients in the age group over 65 years, this association was not maintained. Regarding ethnicity, it was observed that in caucasian patients the highest sodium intake was significantly associated with uncontrolled hypertension

(OR = 23.17; 95% CI: 1.23-147.85); however, among non-caucasians the association was inversely and not statistically significant (Table 4).

**Table 4** - Relationship between resistant and uncontrolled hypertension and sodium intake, stratified by potassium intake, age and ethnicity

Covariables	Resistant and uncontrolled hypertension association with high daily sodium intake		P value
	Crude OR (CI to 95%)	Adjusted OR (CI to 95%)	
Estimated daily Potassium Intake (grams)			
≤ 4,2 (1st tercile)	1,00 (0,07 – 13,86)	1,14 (0,08 – 16,94) <sup>a</sup>	0,93
> 4,2 (2nd and 3rd tercile)	6,33 (1,14 – 13,99)	8,27 (1,12 – 61,16) <sup>a</sup>	0,03
Age (Years)			
40 to 65	7,50 (1,28 – 40,09)	14,91 (1,37 – 162,07) <sup>b</sup>	0,02
> 65	0,88 (0,04 – 14,99)	0,74 (0,06 – 17,10) <sup>b</sup>	0,85
Ethnicity			
Non- caucasian	0,43 (0,04 – 4,81)	0,52 (0,08 – 8,38) <sup>b</sup>	0,64
Caucasian	13,20 (1,23 – 140,67)	23,17 (1,23 – 147,85) <sup>b</sup>	0,03

<sup>a</sup> OR Adjusted for urinary creatinine and BMI

<sup>b</sup> OR Adjusted for sex and BMI

It was found that high potassium intake tends to be statistically associated with RH for patients with daily sodium intake of less than 4 g (OR = 0.05, 95% CI 0.01- 1.00) ( Table 5).

**Table 5** – Relationship between resistant and uncontrolled hypertension and high potassium intake, stratified by sodium intake

Covariable	Association of resistant and uncontrolled hypertension with daily high potassium intake		P value
	Crude OR (CI to 95%)	Adjusted OR (CI to 95%)	
Estimated daily sodium intake (grams)			
< 4,0	0,20 (0,02 – 1,42)	0,05 (0,01 – 1,00) <sup>a</sup>	0,05
≥ 4,0	1,27 (0,10 – 14,94)	0,49 (0,03 – 9,13) <sup>a</sup>	0,63

<sup>a</sup>OR adjusted for age, weight and height.

IV. DISCUSSION

Few studies have investigated the relationship between resistant hypertension and sodium consumption, however, evidence from studies evaluating the association between sodium intake and arterial hypertension has identified a consistent relationship in ecological studies with significant differences between urban and rural populations [16]. Although there are few studies on the prevalence of resistant and uncontrolled hypertension, the data observed in the present study are worrisome, since more than 76.5% of the patients presented high blood pressure levels, even using 03 or more medications.

RH has shown a tendency to increased prevalence in recent years in the United States (Egan et al., 2011), [7] which

has raised concern since population studies have shown the importance of controlling hypertension for reducing cardiovascular morbidity and mortality [17], [18]. It is estimated that only one third of the hypertensive population has a controlled blood pressure, even with current therapeutic strategies [17], [19].

Among the characteristics that predominate in patients with resistant and uncontrolled hypertension, high sodium intake is noteworthy [20], [21]. contributing to increase resistance to antihypertensive therapy [2]. In this sense, it is emphasized that in the present study the proportion (57%) of patients who presented daily sodium intake (4g) twice than the WHO recommendations (2g) [21] was high.

The results of this study also showed that sodium intake equal to or greater than 4 g was a factor associated with resistant and uncontrolled hypertension in the group of patients with the following characteristics: age between 40 and 65 years old; potassium intake above 4.2g, and caucasian ethnicity. These findings remained even after adjustment for possible confounding factors. The reduction of sodium in the diet in hypertensive patients decreases systolic blood pressure from 3.7 to 7 mmHg and diastolic from 0.9 to 2.5 mmHg [23] , [24]. In patients with resistant hypertension, the magnitude of this recommendation is unknown. Therefore, data from this study produced evidence that in individuals with higher intakes of potassium, resistant and uncontrolled hypertension was significantly associated with high sodium intake, however, in the group of patients with low potassium intake, high intake of sodium was not relevant for the occurrence of resistant and uncontrolled hypertension.

These data differ from other studies that have demonstrated a protective role for potassium in relation to high blood pressure levels in hypertensive patients. Thus, in the present study, in the group with low potassium intake, the chances to find a positive association between ingestion of sodium and uncontrolled hypertension should have been higher than in the group with high potassium intake.

Mente et al. (2014) found that high sodium excretion, when combined with low potassium excretion, was significantly associated with a higher blood pressure than in the group of patients who had high sodium excretion combined with elevated potassium excretion [8].

It is known that a higher intake of potassium attenuates the adverse effects of sodium on blood pressure and suggest that the intake of sodium-potassium ratio of 1:1, is considered beneficial. Thus, even potassium-rich diets may not favor lowering blood pressure levels if the amount of sodium in the diet is higher than potassium intake. Potassium is responsible for the reduction of intracellular sodium through the sodium-potassium pump, inducing the fall of blood pressure through increasead natriuresis, decreased renin and norepinephrine, and increased secretion of prostaglandins.

On the other hand, this explanatory mechanism helps to understand the results of the present study, regarding the protective effect of high potassium intake in the occurrence of resistant and uncontrolled hypertension in the group of patients who presented lower sodium intake (intake below 4 g). Similarly, other studies point to the inverse relationship between estimated potassium excretion and blood pressure, even for a possible sodium modulating effect in this association [25] In order to explain this potassium

benefit, a number of mechanisms have been suggested, such as reduction of neural adrenergic activity, decrease of plasma renin levels [26], inhibition of free radical formation [27] and increase of Na<sup>+</sup> / K<sup>+</sup> -ATPase enzyme activity, increasing the cellular uptake of potassium and reducing intracellular sodium [28].

Regarding ethnicity, high sodium intake was significantly associated with resistant and uncontrolled hypertension only among caucasians. Regarding this issue, some studies have already shown that non-Caucasian individuals have a higher sensitivity to sodium when compared to Caucasian individuals [29]. The genetic factors responsible for these different body responses are still not well known in humans. Moffa and Sanches (2001) [30] claim that non-Caucasians tend to have lower plasma renin activity and that these patients may have higher intravascular volumes. Studies have shown that hypertension in non-Caucasians has a higher prevalence, worse evolution and more serious and frequent complications. This aspect may have a correlation with the socioeconomic level of this group of patients. However, the non-association of uncontrolled and resistant hypertension with the high sodium intake in non-Caucasians identified in the present study may be justified in part by the fact that the participating population is strongly miscegenated [19], [31].

Age was a variable that changed the association between resistant and uncontrolled hypertension and high sodium intake (> 4 g / day). This association was only positive in younger patients (40-65 years). In a multicenter study with more than 10,000 participants, it was shown that the relationship between blood pressure and age was stronger in subjects with greater variation in daily salt intake (between 0.12 and 14 g / day). However, it was evident that the curve of the increase in blood pressure with age was more pronounced in locations where salt intake was higher, and blood pressure did not simply increase with higher ages in populations where salt intake was very low, as described in Yanomami Indians in Brazil [23].

Another relevant aspect that may help to understand the results of the present study is that younger patients have been suggested a lower response of blood pressure levels to reduction of sodium consumption when compared to the elderly group. He & MacGregor (2004) [32] found that, unlike normotensive patients, hypertensive elderly responded with weak blood pressure declines to sodium restriction and that the magnitude of tension variation was less significant in the younger populations (40-60 years) [33], [34]. Changes in the lifestyle of the elderly and reduction of sodium intake produced satisfactory benefits in reducing blood pressure levels (p <0.001) [35] - [37].

## V. CONCLUSIONS

We found a high frequency of sodium consumption in RH. We observed an association between adequate blood pressure control and resistant hypertension, and high potassium intake and low sodium levels in patients with lower age and Caucasians. New investigations are necessary to determine the role of sodium, potassium and other risk factors in resistant hypertension, considering that the results of this study suggest a different relationship between sodium, potassium and resistant and uncontrolled hypertension of

those observed in studies investigating these associations with systemic arterial hypertension.

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