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Research Article

Plasma Atrial Natriuretic Peptide Responses to Salt-Loading in Salt-Sensitive and Salt-Resistant Normotensive and Hypertensive Nigerians

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Summary: Salt-sensitivity is more common in blacks than whites but the underlying cause is not fully known. Atrial natriuretic peptide (ANP) concentrations might play a role. This study investigated plasma ANP concentrations and effect of salt-loading in salt-sensitive (SS) and salt-resistant (SR) normotensive (NT) and hypertensive (HT) Nigerians of both genders. Forty-three (43) apparently healthy (NT) adult volunteers and thirty-seven (37) age-matched newly diagnosed (HT) Nigerians were grouped into SS and SR volunteers based on the mean changes in their mean arterial blood pressure ≥ 5 mmHg, following a 5-day administration of 200 mmol of sodium in each of the volunteers. ANP concentrations were determined before and after salt loading. Prevalence of SS and SR in the NT and HT Nigerians was 51.2% and 48.8%, respectively. Basal ANP levels in SS and SR NT and HT participants were similar but salt significantly raised ANP concentrations in SS ($p < 0.01$), SR ($p < 0.001$) NT volunteers only. Besides, basal ANP concentrations observed in SS and SR NT and HT males and females were similar but salt loading significantly increased ANP levels in SS NT males ($p < 0.05$), SR NT ($p < 0.001$) and HT ($p < 0.05$) females only. These findings showed that salt-sensitive hypertensive individuals demonstrated a blunted ANP response to salt loading. However, salt-resistant normotensive volunteers showed a significant increase in ANP concentrations, with higher levels in NT females than males. The impaired ANP response to salt challenge might be the basis for the higher prevalence of salt-sensitivity among blacks.

Keywords*: Salt-sensitivity, salt-resistance, atrial natriuretic peptide, gender and hypertension*

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INTRODUCTION

Hypertension is a chronic disease condition that is influenced by genetic and environmental factors (Kune and Zicha, 2009); and with the recent high consumption of dietary salt in most countries of the world, the prevalence of hypertension has increased tremendously (Choi *et al*., 2015; Dötsch-Klerk *et al*., 2015). Substantial evidence suggests that some individuals can adequately excrete high amounts of salt consumed without an appreciable increase in their arterial blood pressure whereas others cannot (Choi *et al*., 2015; Burnier, 2015). The underlying factor responsible for these differential blood pressure responses to salt loading and renal excretions of salt is not fully understood.

Salt-sensitivity can be simply defined as an increase in mean arterial blood pressure of 5 mmHg or above in response to increased salt intake (Felder *et al*., 2013; Elias *et al*., 2014). It increases with increased age, genetic predisposition, metabolic syndrome and obesity (Rust and Ekmekcioglu, 2017). Blacks are reported to be more salt-sensitive than whites (Burnier, 2008; Sandberg and Ji, 2012), About three-quarter (73%) of hypertensive African-Americans are reported to be salt- sensitive (Svetkey *et al*., 1996) while 25% of normotensive individuals are salt-sensitive (Franco and Oparil, 2006; Richardson *et al*., 2013). The prevalence of salt-sensitivity among adult Nigerians is high as it has been documented that more than 50 %of normotensive Nigerians are salt-sensitive and about 60% of hypertensive counterparts are salt-sensitive (Elias *et al*., 2011). Long-term implication of salt-sensitivity leads to increased mortality in both normotensive and hypertensive humans with no difference in their survival rate (Weinberger, 2002).

However, salt-sensitive hypertensive patients have 3-fold higher cardiovascular events than salt-resistant-hypertensive ones (Morimoto *et al*., 1997; Ehme, 2005). Besides, in males and females of comparable blood pressure values, the damaging effect of increased blood pressure on end organs is far greater in males than in females (Sandberg and Ji, 2012). Although, oestrogen has been documented to play a protective role on cardiovascular function in premenopausal women (Lorga *et al*., 2017), the basis for the greater adverse effect of sustained high blood pressure on the vital organs in males than females, is still a subject of intense research.

Atrial natriuretic peptide (ANP) is a cardiac endocrine hormone that regulates salt and water as well as blood pressure by promoting vasodilation, natriuresis and diuresis (Wang *et al*., 2012). It is secreted primarily from the cardiac atria in response to volume expansion. In mice, abnormally low ANP concentrations cause salt-sensitive hypertension (Song *et al*., 2015). The impaired renal excretory function that is implicated in salt-induced hypertension (Hall, 2016), might be due to abnormal concentrations of ANP in the susceptible individuals. There is paucity of data regarding

ANP concentrations in salt-sensitive normotensive and hypertensive Nigerians.

Hence, this study was designed to investigate plasma ANP concentrations in salt-sensitive and salt-resistant normotensive and hypertensive adult Nigerians, as well as to determine effect of salt and gender on ANP levels in these individuals.

MATERIALS AND METHODS

The study was conducted on forty- three (43) apparently healthy normotensive and thirty- seven (37) age-matched hypertensive volunteers. The number of participants was statistically determined according to the formula prescribed by Eng *et al.,* 2003 for a comparative study. The volunteers were briefed about the experiment and informed consent was obtained. Ethical approval to carry-out the study was obtained from the Health Research Ethic Committee of the College of Medicine, University of Lagos. The participants were divided into salt-sensitive and resistant normotensive and hypertensive groups based on the mean changes in their mean arterial blood pressure (MAP) of 5mmHg or above following 5-day period of salt administration (Weinberger, 1996; Elias *et al.,* 2014).

Inclusion Criteria: The normotensive volunteers that were included in the study had BP < 140/90 mmHg. They were not diabetic or smokers of cigarettes or suffering from any cardiovascular, cerebrovascular or renal disease. The hypertensive volunteers had sustained systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or both (Franklin, 2004). They were not on any antihypertensive drug and not suffering from any complication arising from their sustained elevated blood pressure.

Exclusion Criteria: Volunteers who had severe high blood pressure (BP ≥ 180/110 mmHg), abnormal ECG findings or abnormally high plasma potassium (K ≥ 5.5 mmol) or creatinine levels (Cr ≥ 110μmol/l) were excluded from participating in the study. Pregnant women were also excluded from the study due to medical and ethical reasons. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MABP), plasma atrial natriuretic peptide (ANP), plasma and urinary concentrations of sodium, potassium, urine volumes as well as 24- hour urinary excretions of sodium were determined before and after salt loading in the participants.

Determination of Blood Pressure: Resting blood pressure was determined by auscultatory method, using Accoson Mercury Sphygmomanometer (Accoson, United Kingdom) as per the described instructions of American Heart Association (Beevers *et al*., 2001). Volunteers were allowed to rest for 10 minutes in sitting position before the commencement of measurements. Appropriate cuff sizes were applied based on their mid-arm circumferences. This was ensured so as to prevent under-cuffing or over- cuffing, as this could adversely affect the blood pressure readings. The cuff was wrapped on the right arm of each of the subjects with the midline of bladder over the brachial arterial pulsation.

The cuff bladder was inflated rapidly while palpating radial pulse. Reading at which pulse disappeared was noted, pressure was further elevated by 20-30 mmHg above this value. Then the bladder was slowly deflated while listening for the appearance of Korotkoff's sounds using a stethoscope, placed on the brachial arterial pulsation. Systolic blood pressure and diastolic blood pressure were recorded to the nearest 2mmHg, as the first appearance and disappearance of Korotkoff's sounds, respectively. The blood pressure was measured thrice in each of the participants and average of the readings was determined and recorded.

The mean arterial blood pressure (MABP) was determined from the sum of diastolic blood pressure and one-third of pulse pressure (Zheng *et al*; 2008). The pulse pressure is the difference between systolic and diastolic blood pressure.

Protocol for venous blood collection: Subjects fasted overnight and reported at 9 am in the laboratory for the collection of their venous blood. They were briefed about the procedure. Venous blood was withdrawn from one of the antecubital veins under aseptic condition and emptied into appropriately labeled blood sample bottles. Lithium heparin bottles were used for plasma sodium estimation while chilled EDTA bottles were used for ANP analysis

The withdrawn blood samples were spun immediately at 3,000 rpm at 4ºC for 10 minutes. The supernatants were stored at -40ºC until analyses were carried-out.

Collection of 24-Hour Urine Specimen: The participants were briefed about the procedure and given a 5 litre- plastic keg each to collect their 24-hour voided urine after they had emptied their bladders in the morning. The urine was brought to the laboratory the following day in the morning and measured with a measuring cylinder in order to determine the volumes. Aliquots of the urine were put in the universal bottles and stored at -20^0C until analyses. On the day of analyses, the frozen urinary samples were allowed to thaw at room temperature.

The 24- hour urinary concentrations of sodium and potassium were measured using ion selective electrode (ISE 6000) machine (SFRI, France). The 24- hour urinary excretions of Sodium and potassium were determined by multiplying the concentrations of urinary sodium and potassium in mmol/day by the urinary volumes in litres/day, respectively (Land *et al.,* 2014).

Salt loading in the study Participants: Having determined and recorded the baseline blood pressure and laboratory parameters in the study participants, they ingested a salt load of 200 mmol of sodium each per day in two divided doses for 5 days (Tzemos *et al*; 2008; Elias *et al;* 2014). Compliance of the volunteers with salt ingestion was assessed by determining their 24-hour urinary excretion of sodium before and after salt loading.

Determination of Laboratory Parameters Measured in the study population: The laboratory parameters that were determined in the normotensive and hypertensive subjects were plasma atrial natriuretic peptide (ANP), plasma and urinary concentrations of sodium, potassium as well as 24-hour urinary volumes and excretions of sodium and

potassium. They were determined before and after salt loading in the participants.

Plasma ANP concentrations were determined using Human Atrial Natriuretic Peptide Eliza Kits (Sunlong Biotech, China). The ANP concentrations were analyzed as described by the manufacturer's instructions.

Plasma sodium and potassium concentrations were determined using ion selective electrode (ISE 6000) machine (SFRI, France). The 24- hour urinary volumes and excretions of sodium and potassium were also measured.

Determination of Salt-Sensitivity and Salt-Resistance in the Study Population: The normotensive and the hypertensive volunteers that showed changes of 5 mmHg or greater in their mean arterial blood pressure after salt loading were considered salt-sensitive participants while those that demonstrated less than 5 mmHg were designated, salt- resistant participants (Weinberger, 1996; Elias *et al.*, 2014).

Data Analysis

Data analysis was carried-out with the aid of GraphPad Statistical software, Version 5 for Windows (GraphPad Software, San Diego, California, USA). Data was expressed as mean ± standard error of the mean. The prevalence of salt-sensitivity and resistance in the study groups was expressed in percentages. Variations within or between the salt-sensitive and salt-resistant normotensive and hypertensive volunteers were analyzed using appropriate Student's t- test. Statistical significance was accepted at $p < 0.05$ level.

RESULTS

Effect of Salt Loading on Urinary and Plasma Electrolytes in the Study Population: Table 1 shows urine volumes, plasma and urinary concentrations of sodium and potassium as well as urinary excretions of the electrolytes before and after salt loading in the normotensive and hypertensive volunteers.

The basal values of the urinary and plasma sodium and potassium concentrations observed in the normotensive and hypertensive participants were similar before salt loading. However, after salt loading, urinary sodium concentrations and urinary excretions of sodium in both normotensive and hypertensive volunteers were significantly increased ($p < 0.001$) but plasma sodium concentrations were not elevated in the normotensive subjects but increased ($p < 0.05$) in the hypertensive counterparts.

Besides, plasma concentrations of sodium in the hypertensive participants were significantly higher ($p < 0.05$) than their normotensive volunteers after salt loading. In addition, plasma potassium concentrations were decreased ($p < 0.05$) by salt in the hypertensive volunteers but not significantly in the normotensive counterparts. Furthermore, after acute salt loading, the plasma potassium levels observed in the hypertensive subjects were significantly less ($p < 0.05$) than those of the normotensive colleagues. Besides, urine volumes (output) were increased ($p< 0.05$) by salt challenge in the normotensive volunteers but not significantly in their hypertensive counterparts (Table 1).

Prevalence of Salt-Sensitivity and Salt-Resistance in the Study Population: Table 2 shows the prevalence of salt sensitivity and salt resistance in the normotensive and hypertensive participants. More than half (51.2%) of the normotensive volunteers were salt-sensitive and salt-sensitivity was commoner in males than females (27.9% vs23.3%). The rest (48.8%) of the normotensive volunteers were salt-resistant. In addition, in the normotensive group, females were more salt-resistant than males (30.2% vs 18.6%). In hypertensive group, nearly half (48.6%) of the participants were salt-sensitive. However, salt sensitivity was observed to be more common in females than males (27.0% vs21.6%). The rest (51.4%) of the hypertensive volunteers were salt-resistant. More females than males were found to be salt-resistant (29.7% vs 21.6%, Table 2). Table 2 shows that combination therapy (HU + L-Arg) caused an elevation of antioxidant enzymes levels ($p < 0.001$ in each case) but lowered MDA ($p < 0.001$) and each of the liver enzymes levels ($p < 0.001$ in each case).

Table 1:

Urinary Output, Concentrations and Excretions of Sodium and Potassium and Plasma Levels of Sodium and Potassium before and after Salt Loading in the Study Population

Laboratory Parameters	Normotensive group (n =43)		Hypertensive Group (n = 37)		p Value			
	Before Salt (a)	After Salt (b)	Before Salt (c)	After Salt (d)				
					(a) Vs (b)	(a) vs (c)	(c) vs (d)	(b) vs (d)
PNa (mmol/l)	134.9±0.46	135.3± 0.06	135.7± 0.55	136.7±0.31	NS	NS	< 0.05	< 0.05
PK (mmol/l)	4.56± 0.06	4.53±0.07	4.46± 0.66	4.31± 0.06	NS	NS	< 0.05	< 0.05
24-Hr UV (l)	1.77± 0.11	2.03± 0.12	1.59± 0.13	1.87± 0.11	< 0.05	NS	NS	NS
UNa (mmol/l)	93.15±5.91	132.00±8.33	91.49±6.82	137.3±7.23	< 0.001	NS	< 0.001	NS
UK (mmol/l)	23.31± 2.09	19.54± 1.95	23.85± 2.13	23.30±2.36	NS	NS	NS	NS
UENa (mmol/day)	155.0± 9.56	243.4±14.01	130.8±10.55	246.5±15.63	< 0.001	NS	< 0.001	NS
UEK (mmol/day)	37.49±3.03	34.66±2.63	32.44± 2.77	39.44± 2.89	NS	NS	NS	NS

Values are expressed as Mean ± SEM as analyzed by paired t- test

Key:

PNa = plasma sodium; PK = plasma potassium; UNa= urinary sodium; UK = urinary potassium; 24-Hr UV =24-hour urine volume: UENa = urinary excretion of sodium; UEK = urinary excretion of potassium; before salt = before salt loading; after salt = after salt loading; p< 0.05, p <0.01 and p < 0.001 = significant; NS =not significant

Table 2:
Prevalence of Salt-Sensitivity in the Study Population

	Normotensive Participants		Hypertensive Participants	
Gender	Salt-Sensitive	Salt-Resistant	Salt-Sensitive	Salt-Resistant
Males n, %	12 (27.9%)	8 (18.6%)	8 (21.6%)	8 (21.6%)
Females (n, %)	10 (23.3%)	13 (30.2%)	10 (27.0%)	11 (29.7%)
Total	22 (51.2%)	21 (48.8%)	18 (48.6%)	19 (51.4%)

Values are expressed as numbers and percentages
n = number of participants

ANP Concentrations in Salt-Sensitive and Salt-Resistant Normotensive and Hypertensive Participants: The plasma concentrations of ANP in salt-sensitive and salt-resistant normotensive and hypertensive volunteers are shown in Figure 1. Basal ANP concentrations in salt-sensitive and salt-resistant normotensive and hypertensive participants were similar before salt loading. However, salt significantly elevated ANP levels in salt-sensitive ($p < 0.01$) and salt-resistant ($p < 0.001$) normotensive volunteers.

Besides, the mean change (Δ) in ANP concentrations in salt-resistant normotensive participants was significantly higher ($p < 0.01$) when compared with that of the salt-sensitive normotensive colleagues. (Figure 1). In the hypertensive group of volunteers on the other hand, the basal ANP levels observed in the salt-sensitive and salt-resistant participants, were not significantly different and salt did not significantly raise their ANP levels. Besides the mean changes in their ANP concentrations were similar (Figure 1).

Gender Influence on ANP Concentrations in Salt-Sensitive and Salt- Resistant Normotensive and Hypertensive Participants: Figure 2 shows ANP levels before and after loading in salt-sensitive and salt-resistant male and female normotensive participants. Their basal plasma ANP concentrations were seen to be similar before salt loading, However, salt loading significantly raised ANP levels ($p < 0.05$) in both salt-sensitive and salt-resistant normotensive males. Besides, there was also a significant rise ($p < 0.001$) in ANP concentrations observed in salt-resistant normotensive female volunteers after salt loading but. no significant increase was observed in salt-sensitive normotensive female participants (Figure 2). In the hypertensive subjects on the other hand, the basal ANP levels in salt-sensitive and salt-resistant males and females were not significantly different. However, after salt loading, the ANP levels were significantly raised ($p < 0.05$) in the salt-sensitive hypertensive males and salt- resistance hypertensive females but not significantly in salt-sensitive hypertensive females and salt-resistant hypertensive males (Figure 3).

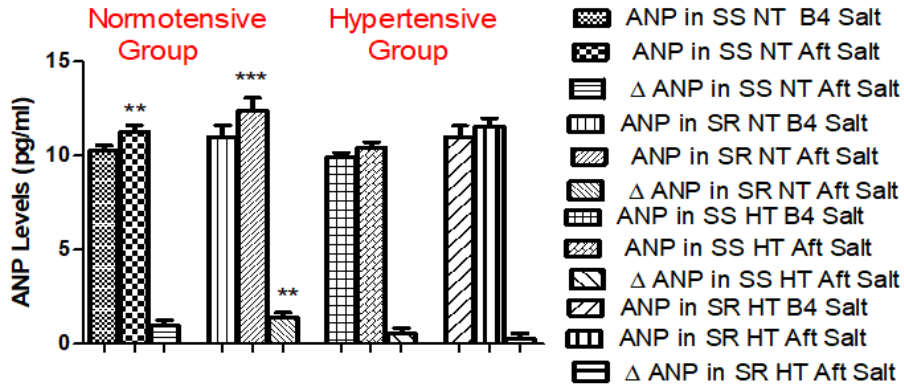

Figure 1
The plasma ANP concentrations in salt-sensitive and salt-resistant normotensive and hypertensive participants before and after salt loading.
NT = normotensive; HT = hypertensive; SS = salt-sensitive; SR = salt-resistant;
Δ = change
B4 salt = before salt loading; Aft salt = after salt loading
** = p< 0.01 between ANP concentration before and after salt loading in SS normotensive participants.
***= p < 0.001between ANP concentrations before and after salt loading in SR normotensive participants.
** = p < 0.01 between the mean changes (Δ) in ANP concentrations after salt loading in SS and SR normotensive participants

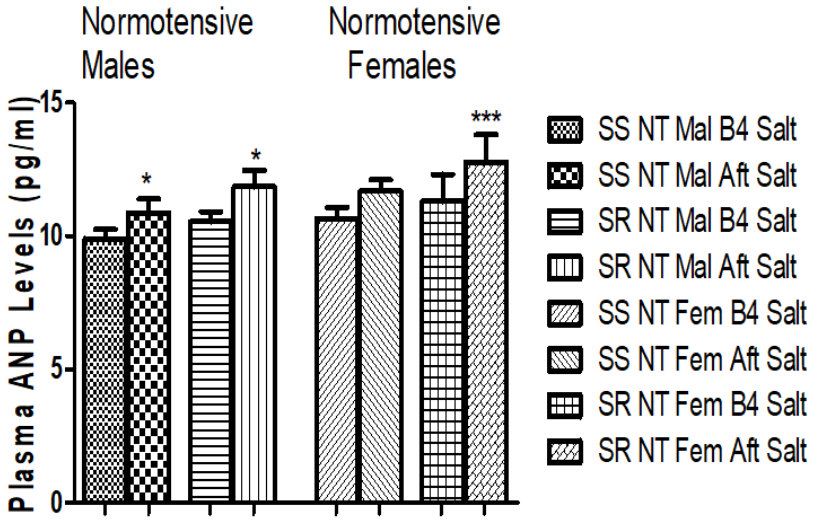

Figure 2
The plasma ANP levels before and after salt loading in salt-sensitive and salt-resistant normotensive male and female participants.
NT = normotensive; SS = salt-sensitive; SR = salt-resistant; Mal = males; Fem = females
B4 salt = before salt loading; Aft salt = after salt loading;
* = p < 0.05 between ANP levels before and after salt loading in salt-sensitive normotensive male participants
* = p < 0.05 between ANP levels before and after salt loading in salt-sensitive normotensive male participants
*** = p < 0.001between ANP levels before and after salt loading in salt-resistant normotensive female participants

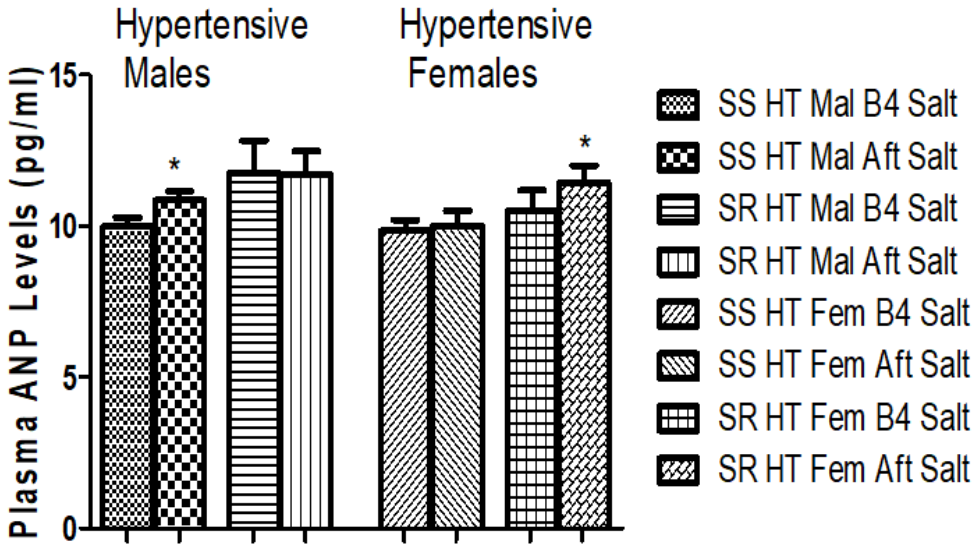

Figure 3
The plasma ANP levels before and after salt loading in salt-sensitive and salt-resistant hypertensive male and female participants
*HT = hypertensive; SS = salt-sensitive; SR = salt-resistant; Δ = change; * = p < 0.05*
B4 salt = before salt loading; Aft salt = after salt loading; Mal = males; Fem = females
** = p < 0.05 between ANP levels before and after salt loading in salt-sensitive hypertensive male participants*
** = p < 0.05 between ANP levels before and after salt loading in salt-resistant hypertensive female participants*

DISCUSSION

The selection of the volunteers was primarily based on their health status. The hypertensive volunteers were newly diagnosed. They did not suffer from any complication arising from their hypertensive state as abnormally high ANP levels have been documented to be seen in heart and kidney diseases (Ogawa et.al, 2015; Volpe *et al*., 2016). In addition, compliance with the salt ingestion by the volunteers was good as evident by the significant increases observed in the 24-hour urinary excretions of sodium in the study population.

Hypertensive volunteers had higher basal plasma sodium levels than their normotensive counterparts. The plasma sodium concentrations in the study population were significantly elevated after salt loading. In addition, the hypertensive subjects had appreciably lower plasma potassium levels than normotensive colleagues following salt loading. High plasma sodium and low plasma potassium concentrations have been implicated in the pathogenesis of hypertension (Abcar and Kujubu, 2009; Perez and Chang, 2014). The increased plasma sodium concentrations and decreased urinary loss of water possibly promoted increases in their blood volumes and cardiac output thereby elevating their arterial blood pressure.

The prevalence of salt-sensitivity as seen in this study population was high, indicating the vulnerability of these salt-sensitive normotensive individuals to the development of salt-sensitive hypertension and cardiovascular disease (Wang *et al*., 2012). Although, the prevalence of salt-sensitivity has been previously documented to be lower in normotensive individuals than hypertensive ones (Franco and Oparil, 2006; Elias *et al*., 2014), the percentage of normotensive volunteers that was observed to be salt-sensitive in this study was slightly higher than that of their hypertensive counterparts. Although, the difference in the prevalence might be due to sample size, it may also stem from increased consumption of salt from various dietary sources which have now become a norm in most countries (Dötsch-Klerk *et al*.,2015).

Nevertheless, in a normotensive state, salt-sensitivity was commoner in males than females whereas the reverse was the case under a hypertensive condition as salt-sensitivity was found to be commoner in hypertensive females than males. The lower prevalence of salt-sensitivity in the normotensive females than males might be due to a protective role that their oestrogen plays on their cardiovascular function (Lorga *et al*., 2017). This protective effect of oestrogen seems to be impaired or attenuated in a hypertensive state. This could be responsible for the higher prevalence of salt-sensitivity that was observed in the hypertensive females.

The basal ANP concentrations in salt-sensitive and salt resistant normotensive and hypertensive adult Nigerian subjects who had not developed any complication from their hypertensive condition, were similar. However, when confronted with salt loading, ANP appreciably rose in the normotensive participants with a greater response in salt-resistant normotensive volunteers but salt-sensitive normotensive and hypertensive volunteers did not show any significant rise.in their ANP levels. The slight increase in ANP concentrations observed in these individuals might be the basis for their salt-sensitivity. Abnormally low ANP has been implicated in pathogenesis of salt-sensitive hypertension in mice (Wang *et al*., 2012; Song *et al*., 2015). Regarding the influence of gender on the plasma ANP concentrations in the study salt-sensitive and salt-resistant normotensive and hypertensive volunteers, salt- resistant normotensive female participants demonstrated greater plasma ANP response to salt loading when compared with their counterpartsalt-sensitive normotensive or hypertensive males. The ANP levels were also found to be higher than that of their salt-resistant hypertensive female colleagues. The gender difference in their ANP concentrations as seen in the normotensive females might also be due to oestrogen effect on the ANP concentrations as it has been reported that

oestrogen induces ANP release from the heart via oestrogen receptor (Vishwakarma *et al*., 2016). However, it is not very clear why salt-sensitive normotensive females demonstrated no significant increase in their ANP levels after salt loading. The slight increase in the plasma ANP levels following salt loading in these normotensive individuals might likely be the cause of their salt-sensitivity.

Though, it is reported and it was also observed in this study that hypertensive participants demonstrated a blunted ANP response to salt loading (Campese *et al*., 1996), this finding was not the case in all the hypertensive volunteers who were salt loaded in this study. Salt-resistant hypertensive females still showed a significant increase in their plasma ANP concentrations after the salt challenge. This implies that the aetiology of hypertension in these hypertensive individuals might not be primarily due to inadequate salt-handing arising from abnormally low ANP levels. The pathogenesis of hypertension in these individuals might be multifactorial.

In conclusion, the study has shown that basal plasma atrial natriuretic peptide levels in salt-sensitive normotensive and hypertensive Nigerians who had not developed any complication were similar but the concentrations of the hormone were significantly raised by salt loading in salt-sensitive and salt-resistant normotensive volunteers with a greater increase in the later. Salt-sensitive hypertensive participants demonstrated blunted ANP response to acute salt-loading. This finding might be the basis for the higher prevalence of salt-sensitivity documented to be seen among blacks

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