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Research Article

Vascular Reactivity and Salt Sensitivity in Normotensive and Hypertensive Adult Nigerians

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ABSTRACT

There are not many studies designed to study the relationship between vascular reactivity and salt sensitivity in a black population. Fifty-two hypertensive (HT) and forty-seven age-matched normotensive (NT) Nigerian subjects took part in the study after informed consent was obtained from them. Ethical clearance was obtained from the College of Medicine of the University of Lagos. Vascular hyperreactivity in response to the Cold Pressor Test (CPT) was determined as a change in systolic blood pressure (ϕSBP) or diastolic blood pressure (ϕDBP) Ó +15mmHg. This was determined before and after salt-loading with 200mmol Na^+/day for 5 days. Salt sensitivty was determined as a change in mean arterial blood pressure (ϕMABP) Ó+5mmHg. Salt-loading led to significant increases in SBP among NT ($p = 0.03$) and among HT ($p = 0.0001$) subjects; DBP increased significantly only among HT subjects ($p = 0.0003$). Systolic and diastolic hyperreactivity were higher among HT (49% and 39% respectively) compared to NT (44% and 39% respectively) at baseline. However systolic hyperreactivity (SHP) increased from 44% to 64% after salt-loading among the NT while diastolic hyperreactivity (DHP) reduced from 39% to 36%. Among the HT, both SHP and DHP reduced from 49% to 33% and from 41% to 31% respectively following salt-loading. Salt sensitivity was higher among HT (56%) compared to NT 34%. Salt sensitivity was positively correlated with systolic reactivity before salt ($r = 0.33$; $p < 0.05$) and after salt ($r = 0.25$; $p > 0.05$) but negatively correlated with diastolic reactivity before salt ($r = -0.38$; $p < 0.05$) and after salt ($r = -0.40$; $p < 0.05$) among NT. These results suggest that systolic hyperreactivity may be a significant determinant in the development of salt sensitive hypertension among this population.

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INTRODUCTION

Hypertension is the leading global risk for mortality the world over and it is responsible for about 12.85% of all deaths worldwide (Mathers, 2009). Approximately one in three adults in the United States suffers from hypertension (Soundararajan, 2010). The figure in Nigeria is no less disturbing and has actually increased over the years. In 1997 the prevalence of hypertension in Nigeria was 16 percent (Cooper, 1997) while Adedoyin *et al.,* (2008), reported a prevalence of 36.6%. Ulasi *et al* (2010) reported 32.8% and Amira et al (2014), 34.8%. Cardiovascular reactivity manifested by the blood pressure and heart rate responses to an externally applied stressor, is an inherited trait and reflects underlying sympathetic system activation (Everson, 2001). Cardiovascular reactivity varies with individual characteristics such as genetic predisposition to disease including a family history of hypertension or other cardiovascular disease; level of stress that the individual is exposed to at work; personality factors and emotion (Everson, 2001). Race is equally important as a determining factor as Blacks

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have been shown to have a higher vascular reactivity to stress (Stein et al, 2000). High pressor and heart rate reactivity have been shown to predispose an individual to the development of hypertension, carotid atherosclerosis and coronary artery disease (Everson et al, 1996). Hyper-reactivity to the Cold Pressor Test (CPT), a powerful stimulus of sympathetic activity that has been used to examine both peripheral and coronary circulation, is considered to be a useful indicator of future hypertension in normotensive individuals (Matthews et al, 2004). This standardised provocative test (Chen et al, 2008) is based on the premise that an excessive blood pressure response to an external stressful stimulus is indicative of future hypertension. It has been suggested that enhanced sympathetic nervous system activity may play a role in the early development of hypertension (Flaa et al, 2008). It has also been suggested that enhanced sympathetic nervous system activity may also play an important role in determining the salt sensitivity of blood pressure (Strazzullo et al, 2001). There has been a lot of attention paid to the relationship of dietary salt intake with the development of hypertension. In spite of the numerous research activity showing that increased salt intake does result in an increase in blood pressure (WHO, 2002, Weinberger, 2004), most of these studies have revealed only a weak relationship between sodium intake/excretion and blood pressure in the general population (Hooper et al, 2002). However, studies have shown some heterogeneity in the response of man to increased dietary salt intake. Individuals who have the propensity to respond with large increases in blood pressure to an increase in salt in the diet are referred to as salt sensitive (Franco & Oparil, 2006). Elias *et al.,* (2011) have reported the presence of salt sensitivity among both normotensive (52%) and hypertensive (61%) Nigerians. However, there are not many studies that are designed to study the relationship between vascular reactivity and salt sensitivity in a black population. This study is therefore designed to determine the association, if any, between vascular reactivity and salt sensitivity among some adult Nigerians living in the Lagos metropolis.

METHODS

Forty-seven (47) normotensive and fifty-two (52) age-matched hypertensive subjects were recruited for this study after informed consent was obtained from them. To be included in the study subjects had to be aged between 25y and 65y, normotensive subjects with SBP <140mmHg and DBP < 90mmHg or hypertensive subjects with SBP Ó140mmHg and/or DBP Ó90mmHg (Joint National Commiteee, 2003). Subjects were free of known cardio-pulmonary and/or neuropathic disease. They were not taking medication that could affect cardiovascular or sympathetic nerve function. Subjects were excluded from the study if they were pregnant or breast feeding or if they had history of poor compliance with medication while they were withdrawn from the study if their plasma creatinine exceeded 200ε mol/L, serum potassium was greater than 5.5mmol/L or their blood pressure was consistently greater than 180mmHg systolic and 110mmHg diastolic.

At the onset of the study, weight (kg) was measured to the nearest 0.1kg with the aid of an Omron Digital body weighing machine and height (m) was measured to the nearest 0.1cm using a stable stadiometer (Seca 217). Body Mass Index (kg/m^2) was calculated from the weight and height (w/h^2). In order to determine whether subjects were normotensive or hypertensive, baseline blood pressure (mmHg) was measured by means of the standardized protocol developed by the International Collaborative Study (Attaman et al, 1996) as follows: appropriate cuff sizes were used based on the middle upper arm circumference of the subjects in order to avoid under-cuffing or over-cuffing; blood pressure measurements were taken on the brachial artery of the right arm; systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded to the nearest 2mmHg as the first and fifth Korotkoff phases respectively. All blood pressure (mmHg) observations were carried out after allowing a 10-minute period of rest in the laboratory. Measurements were carried out by the same observer (SOE) with subjects in the sitting position and using the same Accoson® mercury sphygmomanometer to prevent inter-observation variations.

Experimental Procedure:

Subjects were asked to avoid alcoholic drinks, cigarette smoking, coffee and/or tea as well as exercise on the morning of the experiments (He et al, 2009). On the morning of experiments, baseline measurements were repeated as above.

Determination of salt sensitivty

This was carried out following earlier described methods (Elias et al, 2011). Briefly, after control parameters had been determined (Day 1), subjects ingested a salt load at a dose of 200mmol/day Na^+ as NaCl Analar Grade (BDH, United Kingdom) for 5 days (Coruzzi et al, 2005, Tzemos et al, 2008). The NaCl

had a 99.9% purity (BDH, United Kingdom). The salt was administered in two divided doses and given with 500ml of orange squash daily for 5 days after subjects had eaten in the morning and in the evening. The treatment was well tolerated by all subjects. Subjectsô blood pressure was thereafter determined on the morning of Day 6. Compliance was monitored by means of urinary electrolytes (Todd et al, 2010).

Test of vascular reactivity before and after salt-loading

Subjects were exposed to the Cold Pressor Test (CPT) in order to test for vascular reactivity. After a period of rest of 30 min in the laboratory with room temperature maintained at 22^{o}C (Flaa et al, 2008), blood pressure (mmHg) was determined as described above at 10min intervals until three almost identical blood pressures were obtained. The last of these three was taken to be the Basal Blood Pressure (mmHg) (Woods et al, 1984). The subjectôs right foot was then immersed for 1 minute up to the ankle in ice slurry maintained at 4^{o}C (Strazzullo et al, 2001). Peak Blood Pressure (mmHg) was determined as the highest of three 15sec serial blood pressure readings taken from 1minute after immersion of the foot in ice slurry (Woods et al, 1984). After experiments to determine salt sensitivity following salt-loadinghad been concluded, the subjects were re-exposed to the CPT to determine the effect of salt-loading on vascular reactivity. Basal and Peak BP measurements were again carried out as described earlier.

Monitoring of compliance

Urinary sodium excretion ($U_{Na}.V$) has been shown to provide an accurate index of total sodium intake as it represents approximately 93% of intake at steady-state condition (He & MacGregor, 2003). 24-hour urine samples were obtained as earlier (Elias et al, 2011). The volume was measured and 10ml aliquots saved in the freezer at -80^{o}C until analysed for Na^{+} and K^{+}. Urinary sodium excretion ($U_{Na}.V$(mmol/min)) was calculated before and after salt-loading (Castiglioni et al, 2011).

Ethical Approval

Approval for this study protocol, CM/COM/8/VOL.XXI, was granted by the Research Grants and Experimentation Ethics Committee, College of Medicine of the University of Lagos, Lagos. The study was carried out in accordance with the Helsinski Declaration (WHO, WMA, 2008). All tests were well tolerated by the subjects.

Data analyses

Salt-sensitivity:

This was determined as an increase of Ó5 mmHg in mean arterial blood pressure (MABP) following the salt load, while those with a difference of <5mmHg were considered salt-resistant (SR) (Weinberger, 1996). Subjects were also considered salt-resistant if they showed a reduction in MABP following salt-loading (Weinberger, 1996). Mean arterial blood pressure was calculated from DBP + 1/3 Pulse pressure (mmHg).

Vascular Reactivity:

Subjects were considered hyperreactive if there was a difference of +15mmHg or more between Peak BP and Basal BP whether systolic blood pressure (SBP) or diastolic blood pressure (DBP) (Cooper et al, 1997, Moriyama et al, 2010). The subjects were considered normoreactive if Peak BP minus Basal BP was <15mmHg SBP or DBP (Kasagi et al, 1995, Moriyama et al, 2010).

Magnitude of effect of salt-loading and Cold Pressor Test on MABP of subjects was calculated as percentage change (% qMABP) from baseline values.

Data was analysed with the aid of the Graph Pad Statistical software, Version 5 for Windows (GraphPad Software, San Diego, California, USA). Data are presented as X ± SEM; Student t test was used for comparison and ANOVA was also used with appropriate Post Hoc tests carried out to determine differences among means. Relationships between variables were calculated using regression analysis. Differences were accepted as significant at 95% confidence interval.

RESULTS

Fifty-two hypertensive subjects with a mean age of 44.42±1.28y and forty-seven age-matched control normotensive subjects with mean age 41.23±1.40y participated in the study. The hypertensive subjects weighed more than the normotensive subjects ($p < 0.0001$) and their BMI was also significantly higher ($p < 0.0001$) (Table I). As expected, blood pressure was significantly higher ($p < 0.0001$) among the hypertensive subjects compared with the normotensive subjects (Table I).

Table I: Baseline characteristics of normotensive and hypertensive subjects

	Normotensive (NT) n = 47	**Hypertensive (HT)** n = 52	**p**
Age (y)	41.23 ± 1.40	44.42 ± 1.28	0.12 NS
Weight (kg)	66.28 ± 2.04	78.24 ± 1.74	< 0.0001*
Height (m^2)	1.68 ± 0.02	1.67 ± 0.01	0.37 NS
BMI (kg/m^2)	23.73 ± 0.80	28.59 ± 0.73	< 0.0001*
SBP (mmHg)	117.50 ± 1.54	144.9 ± 2.61	< 0.0001*
DBP (mmHg)	79.74 ± 0.86	95.73 ± 1.50	< 0.0001*
MABP (mmHg)	92.34 ± 0.86	112.3 ± 1.57	< 0.0001*

Key:
BMI = Body Mass Index; NS = not significant; *= significant

Effect of Salt-loading on Blood Pressure:
Salt-loading led to significant increases in SBP among the normotensive subjects from 117.5±1.54 mmHg to 121.1±2.1 mmHg (p = 0.03; Figure 1a) and among the hypertensive subjects from 144.9±2.6 mmHg to 151.9±3.0 mmHg (p = 0.0001; Figure 1b). However, DBP increased significantly only among the hypertensive subjects from 95.73±1.5 mmHg to 100.5± 1.62 mmHg (p = 0.0003; Figure 1b) while there was only a marginal increase among the normotensive subjects (from 79.74±0.9 mmHg to 80.56±1.5 mmHg (p = 0.59; Figure 1a).

Salt sensitivity
55.8% (29/52) of the hypertensive subjects exhibited salt sensitivity while 34.0% (16/47) of the normotensive subjects were salt sensitive.

Blood Pressure Responses to the Cold Pressor Test Before and After Salt-loading:
Thirty-nine of the forty-seven normotensive subjects and fifty-one of the fifty-two hypertensive subjects completed the Cold Pressor Test.

Following exposure to the cold pressor test (CPT), systolic and diastolic blood pressures increased significantly (p < 0.0001) among the normotensive subjects. Systolic blood pressure (SBP) increased from 117.50 ±1.54 mmHg at baseline to 132.20 ± 2.63 mmHg (% difference of 12.53±1.6%), while diastolic blood pressure (DBP) increased from 79.74 ± 2.05 mmHg at baseline to 93.49 ± 1.75 mmHg (% difference of 17.4±2.0%) (Figure 1a). Similarly, among the hypertensive subjects, there were significant increases (p < 0.0001) in SBP from 144.90 ± 2.61 mmHg at baseline to 163.8 ± 3.16 mmHg (% difference of 13.81±1.7%) and in DBP from 95.73 ± 1.50 mmHg at baseline to 110.30 ± 1.83 mmHg (% difference of 14.63±16%) (Figure 1b). After salt-loading, exposure to the CPT caused SBP to increase significanlty (p < 0.0001) from 121.10 ± 2.05 mmHg before exposure to 137.90 ± 2.69 mmHg after exposure (% difference of 14.01±1.5%) (Figure 1a) while DBP increased from 80.56 ± 1.54 mmHg to 94.15 ± 1.82 mmHg (% difference 17.49±2.5%) (Figure 1a). In the same vein, among the hypertensive subjects, there were significant increases (p < 0.0001) in SBP from 151.90 ± 3.04 mmHg before exposure to 171.00 ± 3.23 mmHg (% difference of 12.91±1.6%) (Figure 1b) and in DBP from 100.50 ± 1.62 mmHg to 112.40 ± 1.82 mmHg (% difference of 11.35±1.3%) (Figure 1b). The magnitude of the pressor response to the CPT before and after salt-loading was not significantly different among the normotensive and hypertensive subjects.

Vascular Reactivity before and after salt-loading:
Following exposure to the CPT, 44% (17/39) of the normotensive subjects displayed systolic hyperreactivity (Peak SBP minus Basal SBP Ó 15mmHg) while 39% (15/39) showed diastolic hyperreactivity (Peak DBP minus Basal DBP Ó 15mmHg) to the CPT before salt-loading (Table II). Of the hypertensive subjects, 49% (25/51) showed systolic hyperreactivity while 41% (21/51) showed diastolic hyperreactivity to the CPT before salt-loading (Table II). After salt-loading, exposure to the CPT led to an increase in systolic hyperreactivity from the 43.6% (17/39) before salt-loading to 64.1% (25/39) among the normotensive subjects (Table II). Among the hypertensive subjects on the other hand, there was a decrease in systolic hyperreactivity from the 49.0% (25/51) recorded before salt-loading to 33.3% (17/51) after salt-loading (Table II).

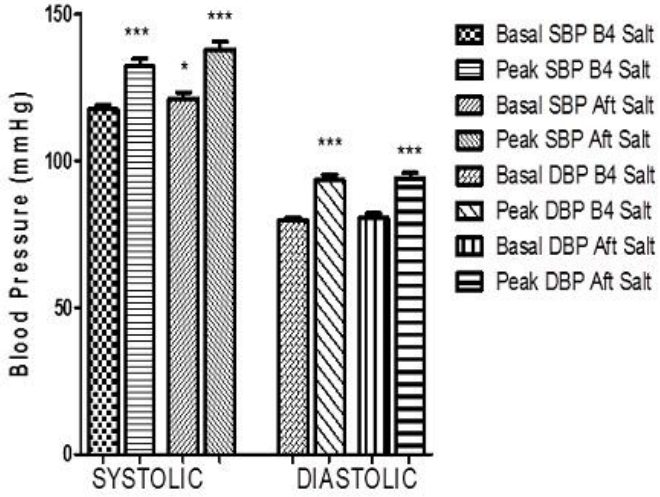

Fig.1a: Pressor responses to the cold pressor test (CPT) in normotensive subjects before and after salt-loading
KEY:
* = p < 0.05 SBP after salt vs before salt
*** = p < 0.0001 Peak BP versus Basal BP
SBP = systolic blood pressure; DBP = diastolic blood pressure
B4 = before; Aft = after;
Basal = Before exposure to CPT; Peak = after exposure to CPT

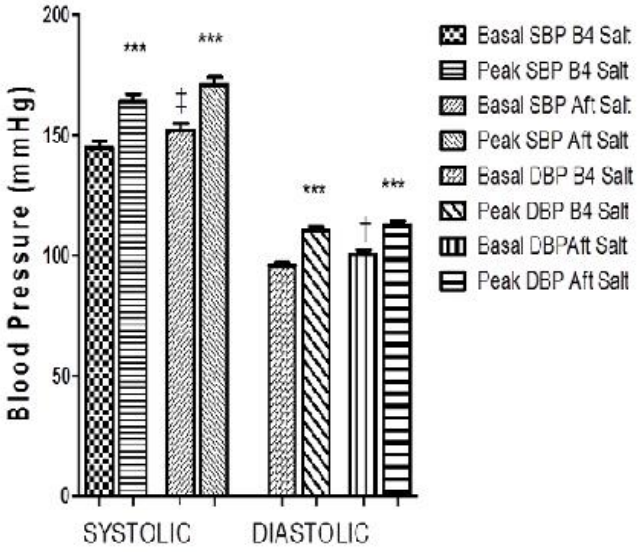

Fig.1b: Pressor responses to the cold pressor test (CPT) in hypertensive subjects before and after salt-loading
KEY:
‡ = p = 0.0001 SBP after salt vs before salt
† = p = 0.0003 DBP after salt vs before salt
*** = p < 0.0001 Peak BP versus Basal BP
SBP = systolic blood pressure; DBP = diastolic blood pressure
B4 = before; Aft = after;
Basal = Before exposure to CPT; Peak = after exposure to CPT

Salt sensitivity and Vascular Reactivity

Among the normotensive subjects, salt sensitivity was positively and significantly correlated with systolic vascular reactivity ($r = 0.33$; $p < 0.05$) but negatively and significantly correlated with diastolic vascular reactivity ($r = -0.38$; $p < 0.05$). On the other hand among hypertensive subjects, salt sensitivity was negatively correlated with both systolic vascular reactivity ($r = -0.008$; $p > 0.05$) and diastolic vascular reactivity ($r = -0.06$; $p > 0.05$).

Urinary Electrolytes

As shown in Table III, urine excretion of sodium ($U_{Na}V$) was 114.6±10.1 mmol/min among the normotensive subjects before salt-loading. This was significantly higher ($p < 0.05$) than the baseline level of 84.4±8.7 mmol/min recorded among the hypertensive subjects. Following salt-loading for 5 days, $U_{Na}V$ increased significantly among the normotensive ($p < 0.01$) and hypertensive ($p < 0.01$) subjects. Urine potassium concentration $U_{(K+)}$ remained constant among the normotensive and hypertensive subjects before and after salt-loading (Table III).

DISCUSSION

That there is a direct causal relationship between salt and blood pressure has been well documented in a number of population studies (He et al, 2009, WHO, 2007). In the present study, we have demonstrated systolic and diastolic hyper-reactivity among Nigerians using the Cold Pressor Test (CPT). Systolic hyper-reactivity was more prominent and more consistently demonstrated than diastolic hyper-reactivity perhaps because systolic blood pressure is more readily affected by temperature changes (Modesi et al, 2013, Robb et al, 2013). This hyperreactivity is an important finding because systolic blood pressure (SBP) reactivity has been associated with increased risk for stroke and this relationship might be because SBP reactivity reflects an acute increase in cardiac force during systole (Everson et al, 2001). It is also possible that stress reactivity leads to the development of hypertension as a result of the direct effect that frequent increases in blood pressure has on the vasculature (Flaa et al, 2008).

Table II: Vascular reactivity among normotensive and hypertensive subjects before and after salt-loading

	SYSTOLIC REACTIVITY		p	DIASTOLIC REACTIVITY		p
	BEFORE SALT	AFTER SALT		BEFORE SALT	AFTER SALT	
NORMOTENSIVE	44% (17/39)	64% (25/39)	0.8	39% (15/39)	36% (14/39)	0.1
HYPERTENSIVE	49% (25/51)	33% (17/51)	0.1	41% (21/51)	31% (16/51)	0.3
p	0.61	0.004		0.79	0.65	

Table III: Urinary Sodium Excretion ($U_{Na}^{+}V$) and Urinary Potassium (U_{K}^{+}) among normotensive and hypertensive subjects before and after salt-loading

	Normotensive (NT) Before Salt	After Salt	p	Hypertensive (HT) Before Salt	After salt	p
$\mathbf{U_{Na}^{+}V}$ (mmol/min)	114.60±10.1	163.0±16.7	0.01	84.4±8.7*	118.2±13.2	0.01
$\mathbf{U_{K}^{+}}$ (mmol/L)	13.70±1.75	13.25±1.74	>0.05	10.05±0.95	9.89±1.20	>0.05

Data are expressed as Mean±S.E.M.

* p <0.05 NT Before Salt versus HT Before Salt

Repeated episodes of elevated BP or deranged haemodynamics occurs in hyperreactive persons as they go about their normal activities, so that over a period of time, their tonic blood pressure rises and this eventually leads to sustained hypertension (Steptoe, 2007). With repeated or prolonged exposure to stress as is present in the Nigerian environment, more persons with systolic hyperreactivity may be more predisposed not only to hypertension but also to other cardiovascular events like stroke. Indeed following a meta-analysis of various studies on cardiovascular reactivity and its effect on clinical outcomes, a 23% increase in risk of hypertension has been observed in persons with higher reactivity scores (Chida & Steptoe, 2010). The present results show higher SBP reactivity in the normotensive subjects before and after salt-loading. However, our results are at variance with an earlier study in which subjects with higher SBP reactivity had higher baseline blood pressure (Chen et al, 2008). It is not clear why there is a reduction in vascular reactivity in the hypertensive subjects following salt-loading. It has been suggested that hypertension on its own causes an endogenous endothelial dysfunction while salt-loading has been shown to cause reduced arterial compliance (Sanders, 2008). Increased dietary salt intake in rats has been shown to cause endothelial dysfunction (Adegunloye & Sofola, 1998, Sofola et al, 2002) as well as increased production of transforming growth factor (TGF) -ϐ1, a fibrogenic factor that promotes decreased conduit artery compliance as well as hypertension (Menneton et al, 2005). These might explain why following salt-loading in the hypertensive subjects in this study, the cold pressor test (CPT) could not cause as much vasoconstriction as it did in the same subjects before salt-loading. This may also account for why the effect of the CPT was less in hypertensive subjects following salt-loading when compared with the effect in normotensive subjects.

There seemed to be a relationship between salt-sensitivity and reactivity status of the subjects. This is consistent with earlier reports among a Chinese population (Chen et al, 2008) among whom was found a significant relationship between salt-sensitivity and hyper-reactivity to the CPT. Results of the correlation analysis in the present study show that vascular reactivity, especially systolic reactivity, is positively correlated to salt sensitivity especially in the normotensive subjects before salt-loading. The fact that the correlation was not significant among the hypertensive subjects may be a pointer to the non-blood pressure effects of dietary salt-loading and indeed salt sensitivity on vascular reactivity (Todd et al, 2010). The observation that 67% of salt-sensitive

normotensive subjects were also hyper-reactive is important in that these subjects have a greater risk for hypertension as well as other cardiovascular events like stroke and increased mortality. It is suggested that this group of subjects will benefit from dietary intervention especially a low sodium diet.

The present study is also important in that identifying the salt sensitivity status of individuals will enable targeted lifestyle modifications of such persons in order to prevent the onset of, or moderate the course of, hypertension in such persons. This is important, considering the fact that mortality in salt-sensitive individuals are similar irrespective of their blood pressure status (Weinberger et al, 2001). As shown by the results of the Dietary Approaches to Stop Hypertension (DASH)- Sodium trial (Sacks et al, 2001), when sodium intake was reduced by approximately 100mmol/d, systolic blood pressure was reduced by a mean of 6.7 mmHg overall; by a mean of 8.3 mmHg in hypertensives and a mean of 5.6 mmHg in normotensives (Sacks et al, 2001). The present results therefore support the fact that although dietary salt reduction is difficult to achieve in the population, it is achievable and worthwhile when targeted at susceptible individuals.

Conclusion

Both groups of normotensive and hypertensive subjects in the present study showed high degree of systolic hyper-reactivity compared to diastolic hyper-reactivity and there was a positive correlation between systolic reactivity and salt-sensitivity among Nigerians. Our results suggest that systolic BP response to the CPT is likely to be useful as a predictive test for the future development of hypertension in normotensive Nigerians and those with pre-hypertension. However, more studies are required for this to be better defined.

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