Plasma Catecholamines in Nigerians with Primary Hypertension

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Background: Hypertension is the most common cardiovascular disease worldwide and is a major cause of morbidity and mortality. Increased adrenergic activity is thought to play a major role in the initiation and progression of the hypertensive state. Hypertension is more severe in Blacks when compared with White patients. Much of the evidence for the increased adrenergic activity is from studies in predominantly White participants. This study aims to evaluate the adrenergic system in Black Nigerian hypertensives by measuring their plasma catecholamines.

Methods: Eighty-two newly diagnosed hypertensives and 51 normal controls were recruited for the study. Blood was obtained from the participants after an overnight fast. Also, a 24-hr urine collection was obtained. Levels of plasma noradrenaline, adrenaline, renin, angiotensin converting enzyme (ACE), atrial natriuretic peptide (ANP), aldosterone and insulin levels were determined using HPLC. Fasting plasma glucose was also determined.

Results: Plasma noradrenaline level was higher while plasma adrenaline level was lower in the hypertensives. The hypertensives also had lower levels of plasma renin, ACE, and ANP. Systolic blood pressure negatively correlated with plasma adrenaline ($r=-0.29$, $P<.001$) and positively correlated with plasma noradrenaline ($r=0.31$, $P<.001$). Renin and ANP also correlated negatively with blood pressure ($r=-0.22$, $P=.012$ and $r=-0.34$, $P<.0001$ respectively).

Conclusions: Black Nigerian hypertensives demonstrate elevated levels of plasma noradrenaline when compared with normal controls. This is consistent with the hypothesis of the hyperadrenergic state in hypertension. Further studies are needed to relate the hyperadrenergic state to the racial differences in the severity of hypertension. (*Ethn Dis*. 2011;21(2):158–162)

Key Words: Hypertension, Adrenergic System, Catecholamine, Blacks, Nigerians

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Introduction

Hypertension is the most common cardiovascular disease in Nigerians and is a major cause of morbidity and mortality worldwide.[1] Hypertension is more severe and associated with more severe sequelae in Blacks when compared with White patients.[2–5] The excess mortality in Blacks due to heart disease, renal failure, and stroke is directly related to the excess burden of hypertension.[6]

The precise etiology and pathophysiology of the primary hypertension however remains unclear but an interplay of genetic and endocrine factors has been implicated.[7–9] The understanding of the role of the sympathetic system in the etiology and pathogenesis of hypertension has undergone several changes. Earlier studies in animals documented conclusively that adrenergic mechanisms were involved in the development and maintenance of experimental hypertension.[10] However, earlier clinical studies based on the measurement of plasma catecholamines did not conclusively demonstrate the role of sympathetic activation in human hypertension.[11] With further advancement in the assessment of sympathetic system, it has been demonstrated that sympathetic activation accompanies hypertension and that the magnitude of sympathetic activation is positively correlated with the magnitude of the blood pressure increase.[12] Furthermore, the degree of sympathetic activation has also been related to the degree of metabolic abnormalities that accompany the hypertensive state.

Given this recent change in the understanding of the role of the sympathetic system in hypertension, the fact that the morbidity and mortality of hypertension is higher in Black patients, and that very few of the previous studies considered ethnic differences in the evaluation of the sympathetic system in hypertension, we therefore sought to evaluate the adrenergic system in Nigerian patients by measuring their plasma catecholamine levels.

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Methods

Participants

Participants were newly diagnosed but untreated hypertensive patients recruited from: the clinics of the University College Hospital, Ibadan; through community screening exercises; and from among the staff of the University College Hospital Ibadan. Patients with secondary hypertension, diabetes mellitus, symptomatic heart failure and chronic kidney disease were excluded. Informed consent was obtained from each participant and ethical approval was obtained from the joint Institutional Review Board of the College of Medicine, University of Ibadan/ University College Hospital, Ibadan, Nigeria.

Table 1. Clinical characteristics of the participants, mean (SD)

Parameter	Normal (*n*=51)	Hypertensive (*n*=82)	*P*
Age, years	47.8 (11.209)	49.83 (10.962)	.3396
Weight, kg	73.27 (16.112)	74.57 (13.651)	.4098
Height, cm	165.63 (8.836)	167.29 (8.433)	.2790
Body mass index, kg/m^2	26.65 (5.134)	26.66 (4.654)	.9668
Pulse, BPM	71.47 (12.782)	75.3 (12.62)	.0567
Systolic blood pressure, mm Hg	127.19 (10.401)	165.45 (15.452)	.0000
Diastolic blood pressure, mm Hg	76.5 (7.733)	95.62 (7.137)	.0000
Pulse pressure, mm Hg	50.69 (8.098)	69.83 (15.452)	.0000
Mean arterial pressure, mm Hg	93.39 (7.833)	118.89 (7.778)	.0000

Data Collection

Blood samples were obtained in the morning after an overnight fast. No caffeine, alcohol or smoking was allowed for at least 2h prior to sampling. Participants were not on any medications prior to sample collection. Blood was collected, after participants' 30 minutes of rest in the supine position, into test tubes stored on ice. Plasma and serum were obtained following rapid centrifugation. A 24-h collection of urine was made the preceding day and stored in plastic containers containing HCl (80 mmol/L final concentration). Participants noted the start and end of the collection time. The amount of urine was quantified at return of the containers. All samples were stored at −70°C until further analyses.

Biochemical and Hormonal Analyses

High-performance (cation exchange) liquid chromatography (HPLC) was used to determine the plasma renin, serum angiotensin converting enzyme level, plasma aldosterone, plasma adrenaline and noradrenaline levels and fasting plasma glucose levels. Urinary VMA level was also analyzed using HPLC. Plasma and urinary sodium and potassium concentrations were measured using a flame photometric method. Plasma and urinary creatinine levels were also determined using standard methods.

To ascertain compliance in the collection of urine, determination of creatinine in the collected urine was also performed, by standard procedures, and catecholamines to creatinine ratios in urine were calculated. Plasma glucose was analyzed by the glucose oxidase method. The homeostasis model assessment (HOMA) described by Matthews et al[13] was used to determine insulin sensitivity, using the formula (fasting glucose in mmol/L x fasting insulin in mU/mL)/22.5.

Statistical Methods

Data from continuous variables are presented as mean (SD) while categoric data are expressed as percentages. All statistical tests were two-sided and carried out to a significance level of .05. Normality of continuous variables was assessed by the Shapiro-Wilks test. Student *t* test for independent groups was used to compare normal continuous data while Mann-Whitney test was used to compare non-normal data. The statistical program used was R, Version 2.10.0.[14]

RESULTS

Eighty-two hypertensive and 51 controls were studied. As shown in Table 1, age and anthropometric indices of the participants were similar. Table 2 describes the biochemical and hormonal values in the groups while Figures 1 and 2 show distribution of plasma catecholamines in the groups. There were no differences in levels of: plasma sodium and potassium; plasma creatinine and urinary creatinine; and 24-hr urinary excretion of sodium and potassium. Fasting plasma glucose and insulin levels were similar in the two groups. There was no difference in the insulin sensitivity as assessed by HOMA-IR between the two groups. The hypertensive participants had lower levels of plasma renin, angiotensin converting enzyme, and atrial natriuretic peptide. Also, levels of plasma adrenaline were lower in the hypertensive patients while noradrenaline levels were higher.

Systolic blood pressure negatively correlated with plasma adrenaline level ($r=-0.29$, $P<.001$) and positively correlated with plasma noradrenaline levels ($r=0.31$, $P<.001$). Renin and atrial natriuretic peptide also correlated negatively with blood pressure ($r=-0.22$, $P=.012$ and $r=-0.34$, $P<.0001$ respectively). There was no bivariate relationship between aldosterone, angiotensin converting enzyme and insulin levels and blood pressure. Similarly, no relationship existed between plasma electrolytes and 24-hr urinary electrolytes, as well as 24-hr urinary VMA and blood pressure.

DISCUSSION

In our study, we found that newly diagnosed hypertensive subjects had elevated plasma noradrenaline but lower plasma adrenaline levels. Levels of renin, atrial natriuretic peptide and angiotensin converting enzyme were lower in the hypertensive group. Aldosterone levels were similar between the two groups.

The finding of elevated noradrenaline levels in the hypertensive participants in this study is in keeping with

Table 2. Biochemical and hormonal parameters of the participants – mean (SD)

Parameter	Normal controls	Hypertensive	*P*
Sodium, mmol/L	139.58 (6.591)	137.94(5.667)	.1638
Potassium, mmol/L	4.11 (.775)	4.02 (.801)	.5814
Creatinine, mg/dL	1.07 (.559)	1.1 (.555)	.9571
Urinary sodium, mmol/L	63.33 (40.538)	68.35 (41.173)	.4968
Urinary sodium excretion, mmol/24hr	90.77 (50.873)	103.93 (63.571)	.4508
Urinary potassium excretion, mmol/24hr	20.44 (14.761)	24.04 (16.527)	.1863
Urinary potassium, mmol/L	13.99 (10.782)	16.06 (10.544)	.2036
Urinary creatinine, mg/dL	50.45 (44.27)	53.73 (43.967)	.6535
Plasma renin, ng/mL	2.52 (.834)	2.1 (.697)	.0007
Plasma angiotensin converting enzyme, U/L	2.38 (1.662)	2.03 (1.489)	.0147
Plasma atrial natriuretic peptide, U/L	5.63 (2.223)	4.22 (2.274)	.0006
Plasma aldosterone, nmol/L	.26 (.058)	.25 (.059)	.1162
Plasma adrenaline, pmol/L	28.12 (13.878)	19.14 (15.994)	.0004
Plasma noradrenaline, pmol/L	416.2 (326.369)	651.66 (322.789)	.0001
Urinary VMA, μg/mg	3.9 (3.702)	2.87 (2.767)	.77
Plasma insulin, μU/L	2.94 (.901)	2.63 (.61)	.1267
HOMA-IR*	.54 (.192)	.5 (.157)	.3929
Fasting plasma glucose, mg/dL	73.64 (11.656)	77.04 (16.577)	.5351

* HOMA-IR is calculated by the formula: fasting glucose in mmol/L x fasting insulin in mU/mL)/22.5

previous studies[11,15] and supports the hypothesis that activation of the sympathoadrenergic system might play a dominant role in the genesis of hypertension.[12] Several methods have been developed in the evaluation of the adrenergic system in hypertension and these have ranged from the measurement of the plasma levels of catecholamines to the direct assessment of human sympathetic function with methods such as noradrenaline radiolabeled spillover technique, the microneurographic recording of efferent postganglionic muscle sympathetic nerve firing rate and power spectral analysis of heart rate signal. These studies have provided evidence that suggests that sympathetic overdrive is a hallmark of hypertension of essential nature.[12]

The mechanism of the excess adrenergic overdrive has, however, not been completely elucidated. Some of the suggested hypotheses would include the impairment of baroreflex control of vagal and sympathetic influences to the heart and the peripheral circulation favoring potentiation of adrenergic drive to peripheral vessels;[16] or the possibility of impairment of reflexes stemming from the volume-sensitive receptors located in the cardiopulmonary region, which tonically restrain adrenergic flow.[17] The negative correlation of plasma adrenaline levels with blood pressure would indicate suppression of production of catecholamines by the adrenal gland due to the higher than normal levels of plasma noradrenaline.

Evidence also seems to suggest that the metabolic disarray frequently observed in hypertension could be related

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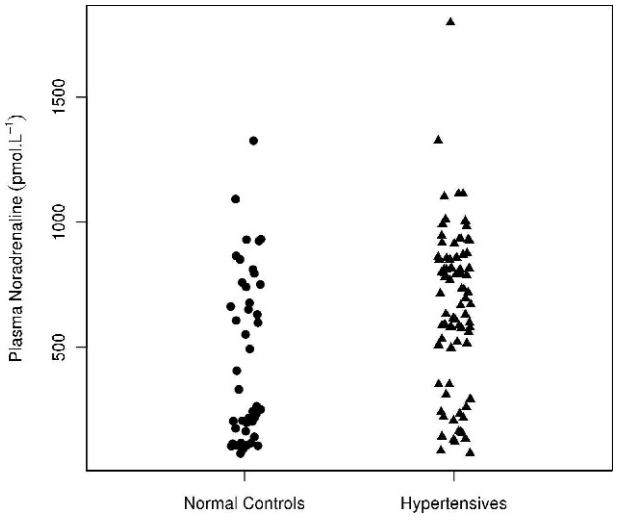

Fig 1. Noradrenaline levels in the hypertensives and control participants

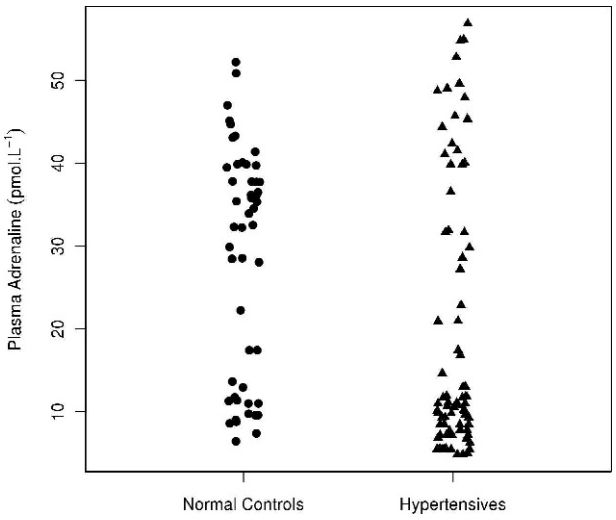

Fig 2. Adrenaline levels in the hypertensives and control participants

to the sympathetic overdrive. It has been observed that insulin leads to a marked stimulation of the sympathetic system.[18,19] In contrast, a longitudinal study among young nonobese Japanese patients demonstrated that sympathetic nerve hyperactivity appears to precede hyperinsulinaemia and blood pressure elevation.[20] These would suggest a complex relationship between hyperinsulinaemia and sympathetic activity. However, in this present study, there were no differences in the levels of fasting plasma insulin and insulin resistance between the hypertensive participants and the controls.

Findings from this study support previous studies that had established lower renin levels in Black hypertensives.[21,22] The lower renin, angiotensin converting enzyme, and atrial natriuretic peptide levels observed in this study could also be as a result of a negative feedback mechanism from the heightened adrenergic activity suppressing other counter-regulatory hormones. An earlier study[23] that compared ethnic differences in plasma catecholamines found no difference in the levels of plasma noradrenaline despite lower plasma renin activity among Blacks. The racial differences in the severity of hypertension might be related to differences in response to the hyperadrenergic hypertensive state.

Studies have shown wide intra-individual variability of plasma levels of catecholamines.[24] This could be a limitation of this study as only one measurement of the plasma catecholamines was obtained in the participants.

In conclusion, Black hypertensives demonstrate elevated levels of plasma noradrenaline when compared with normal controls. This finding is consistent with the hypothesis of the hyperadrenergic state in hypertension. Further studies are needed to relate the hyperadrenergic state to the racial differences in the severity of hypertension. It would also be necessary to relate the hyperadrenergic state to the severity of hypertension in Black patients.

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AUTHOR CONTRIBUTIONS

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Data analysis and interpretation: Adebiyi, Akinosun
Manuscript draft: Adebiyi, Akinosun, Nwafor, Falase
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Acquisition of funding: Adebiyi, Falase
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