ORIGINAL ARTICLE

Left Ventricular Systolic Dysfunction in Asymptomatic Black Hypertensive Subjects

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BACKGROUND
Hypertension has been established as one of the commonest causes of heart failure especially in sub-Saharan Africa. We have previously observed a high prevalence of left ventricular (LV) systolic dysfunction in hypertensive heart failure patients in Nigeria despite a low prevalence of ischemic heart disease. The present study was, therefore, undertaken to assess the prevalence of asymptomatic LV systolic dysfunction in hypertensive black African subjects with no history of heart failure.

METHODS
One thousand nine hundred forty-seven hypertensive subjects without heart failure presenting to the Cardiology Unit, Department of Medicine, University of Abuja Teaching Hospital, Nigeria, from April 2006 to August 2013 had clinical and echocardiographic evaluation.

RESULTS
Nine hundred fifty-three (48.9%) were males and 994 (51.1%) were females. One thousand eight hundred seventeen (93.3%) had normal LV systolic function (LV ejection fraction (LVEF) ≥ 54%), 68 (3.5%) had

mild LV systolic dysfunction (LVEF 45–54%), 43 (2.3%) had moderate LV systolic dysfunction (LVEF 30–44%), and 16 (0.9%) had severe LV systolic dysfunction (LVEF < 30%). Male subjects had worse LV systolic function compared to women (mean LVEF 73.2% vs. 75.6%, P value < 0.0001) and diabetic subjects had worse LV systolic function compared to nondiabetic subjects (LVEF 72.3% vs. 75.7%, $P = 0.02$). In multivariate regression analysis, lower LVEF as a continuous variable was associated with older age, male sex, diabetes mellitus, LV mass indexed for body surface area, diastolic blood pressure, posterior wall thickness in diastole, left atrial diameter, and LV internal diameter in diastole.

CONCLUSIONS
In a cohort of asymptomatic Black hypertensive subjects, 6.7% had LV systolic dysfunction, which was associated with male gender, diabetes mellitus, and larger LV mass.

Keywords: blood pressure; hypertension; left ventricular; systolic dysfunction.

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Hypertension is a well recognized cause of heart failure, and most patients who develop heart failure have a prior history of hypertension.[1] In the Framingham Heart Study, hypertension accounted for 39% of heart failure in men and 59% in women.[2–4] In the Global Burden of Disease 2010 Project,[5] hypertensive heart disease, which comprises hypertension, hypertension with LV hypertrophy, and hypertensive heart failure, was ranked one of the most common causes of disability-adjusted life years. A recent survey of the causes, treatments, and outcomes of acute heart failure in 1,006 Africans from 9 sub-Saharan Africa countries identified that heart failure was due to hypertension in 45% of subjects.[6] Previous studies in the sub-Saharan African population have reported similar findings. For example, hypertension was found to be the leading cause of heart failure in Nigeria and Cameroon, accounting for approximately 60% and 54% of cases, respectively.[7,8] Furthermore, hypertensive

heart failure was the most frequent type of heart failure reported in the Heart of Soweto study accounting for one third of cases.[9] More recently, in the Abuja Heart Study in Nigeria,[10] hypertensive heart failure comprised 60% of cases.

In addition, asymptomatic LV systolic dysfunction has been previously reported in the setting of hypertension, and in a population-based cohort, it was associated with male gender, black race, diabetes, and higher LV mass.[11] However, this was in the setting of a high prevalence of ischemic heart disease and other cardiovascular risk factors, which may confound the association with hypertension and LV systolic dysfunction. The present study was, therefore, undertaken to assess the prevalence of asymptomatic LV systolic dysfunction in hypertensive black African subjects in Nigeria, where the prevalence of ischemic heart disease and other cardiovascular risk factors is relatively low.

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METHODS

This is a prospective cohort study of new outpatients presenting to the Cardiology Clinic of University of Abuja Teaching Hospital, Gwagwalada, Abuja, Nigeria, with a diagnosis of hypertension from April 2006 to August 2013. Two thousand one subjects were initially recruited for the study, while 1,947 were finally enrolled. These patients were new referrals with hypertension from both family and general physicians. The diagnosis of hypertension was according to the guidelines of the Joint National Committee.[12] Subjects with a clinical history of angina, myocardial infarction, heart failure, stroke, diabetes, or chronic kidney disease; clinical symptoms or signs of heart failure; ECG features of myocardial infarction; elevated cardiac troponin I (>0.5 ng/ml); serum creatinine greater than 2 mg/dl; or regional wall motion abnormalities on the transthoracic echocardiogram were excluded. This comprised 2.7% of the total number of subjects initially recruited.

We obtained detailed clinical data using a standardized questionnaire given to the subjects on entry. This study complied with the Declaration of Helsinki and all participants provided written informed consent and the study was approved by the University of Abuja Teaching Hospital Ethics Committee.

Each subject had fasting blood sugar, fasting lipid profile, electrolytes, urea and creatinine, and full blood count assessed.

Transthoracic echocardiography

Echocardiography was performed using a commercially available ultrasound system (IVIS-60 and Vivid E). Subjects were examined in the left lateral decubitus position using standard parasternal, short-axis, and apical views. Studies were performed according to the recommendations of the American Society of Echocardiography by an experienced echocardiographer. Measurements were averaged over 3 cardiac cycles. The LV measurements taken include interventricular septal thickness at end diastole (IVSTd), posterior wall thickness at end diastole (PWTd), the left ventricular internal diameter in diastole (LVIDD), and left ventricular internal diameter in systole. LV systolic function was calculated by Teichholz's formula.[13] LV mass was calculated using the formula: LV mass = 0.8 [1.04(IVSTd + LVIDD + PWTd)3 + 0.6 g]. This yields values closely related to necropsy LV weight with excellent interstudy reproducibility ($r = 0.90$).[14] LV mass was considered to be increased when LV mass index exceeded 49.2 g/m$^{2.7}$ in men and 46.7 g/m$^{2.7}$ in women.[15] Relative wall thickness was calculated as 2 × PWTd/LVIDD.

Subjects were categorized into 4 groups according to their LV ejection fraction[16]: normal LV systolic function (LV ejection fraction (LVEF) > 54%), mild LV systolic dysfunction (LVEF = 41–54%), moderate LV systolic function (LVEF = 30–44%), and severe LV systolic dysfunction (LVEF ≤ 40%). Diastolic function was assessed using both transmitral flow and Tissue Doppler imaging.

Statistical analysis

Data were analyzed using SPSS version 16.0 Software (SPSS, Chicago, IL). Continuous variables were expressed as mean ± SD, while categorical variables were expressed as percentages. Comparison between 2 groups was assessed with Student's t-test for independent variables. Analysis of variance with Scheffe's *post hoc* test was used for comparisons between multiple groups. Multivariate linear regression analysis was performed with LVEF as dependent variable with inclusion of demographic and echocardiography parameters. A 2-tailed P value of 0.05 was considered statistically significant.

RESULTS

Clinical and demographic characteristics of the subjects categorized according to LV systolic function

Table 1 shows the clinical and demographic characteristics of the 3 groups of subjects categorized by their LV systolic function. Subjects with normal LV systolic function had significantly higher body mass index compared to those with mild and moderate–severe LV systolic dysfunction and significantly higher pulse pressure compared to those with severe LV systolic dysfunction. There was no significant difference in the age, mean arterial pressure, fasting blood sugar, lipid profile, and packed cell volume among the groups.

Echocardiographic characteristics of the subjects categorized according to LV systolic function

As described in Table 2, the left atrial diameter, left atrial area, LV internal diameter in both diastole and systole, and LV mass either indexed or not were highest in subjects with severe LV systolic dysfunction and smallest in those with normal LV systolic function. The LV wall thickness and relative wall thickness were higher in subjects with mild LV systolic function compared to subjects with normal and moderate–severe LV systolic dysfunction. Subjects with severe LV systolic dysfunction had the worst diastolic function (highest E/e').

Comparison of echocardiographic parameters in male and female subjects

Table 3 shows that male subjects had significantly higher right ventricular diameter, aortic root diameter, left atrial diameter, LV wall thickness, LVIDD, and LV mass indexed for body surface area when compared with female subjects. They, however, had significantly lower LV ejection fraction when compared with the female subjects.

Multivariate analysis of independent covariates associated with LV ejection fraction

Table 4 shows that low LV ejection correlated with age, male sex, diabetes mellitus, body mass index, diastolic blood pressure, left atrial diameter, LVIDD, PWTd, and LV mass indexed for body surface area.

DISCUSSION

This study represents one of the largest comprehensive assessments of the prevalence and correlates of LV systolic

Table 1. Clinical and demographic characteristics of subjects categorized according to LV systolic function

Variable	Normal LV systolic function (N = 1,817)	Mild LV systolic dysfunction (N = 68)	Moderate and severe LV systolic dysfunction (N = 59)	P value
Age (years)	51.8±12.6	52.3±14.0	55.4±14.8	NS
BMI (kg/m^2)	28.5±7.0	25.9±5.1	25.9±5.1	<0.001
Smoking habits (%)	170 (9.3)	6 (9.5)	9.7 (6)	NS
SBP (mm Hg)	151±21	150±21	149.0±21	NS
DBP (mm Hg)	102±13	101±15	100±15	NS
PP (mm Hg)	51±17	48±16	45.6±20	0.03
MAP (mm Hg)	111±19	109±17	108±17	0.08
FBS (mmol/l)	4.8±0.55	4.9±0.60	4.9±0.5	NS
TC (mmol/l)	5.0±0.9	4.7±1.1	4.6±1.0	NS
TC > 5.2 mmol/l (%)	416 (22.9)	15 (22.4)	13 (22.1)	NS
LDL cholesterol (mmol/l)	3.2±0.8	3.1±0.9	3.0±0.8	NS
HDL cholesterol (mmol/l)	1.3±0.4	1.2±0.3	1.2±0.2	NS
Triglyceride (mmol/l)	1.4±0.7	1.3±0.5	1.2±0.6	NS
PCV (%)	39.3±3.5	39.2±4.2	39.0±5.5	NS

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FBS, fasting blood sugar; HDL, high density lipoprotein; LDL, low density lipoprotein; MAP, mean arterial pressure; PCV, packed cell volume; PP, pulse pressure; SBP, systolic blood pressure; TC, total cholesterol.

Table 2. Echocardiographic characteristics of subjects categorized according to LV systolic function

Variable	Normal LV systolic function (N = 1,817)	Mild LV systolic dysfunction (N = 68)	Moderate and severe LV systolic dysfunction (N = 59)	P value
RVD (cm)	3.1±0.43	3.0±0.52	3.2±0.68	NS
Aorta (cm)	3.0±0.38	3.1±0.47	3.2±0.68	NS
LAD (cm)	3.5±0.62	4.0±0.74[a]	4.3±0.84[a]	<0.001
LAA (cm^2)	16.8±4.5	19.7±5.9[a]	23.9±9.1[a,b]	<0.001
IVSTd (cm)	1.1±0.24	1.3±0.26[a,c]	0.97±0.26	<0.001
PWTd (cm)	1.1±0.33	1.4±0.39[a,c]	0.98±0.22	<0.001
LVIDD (cm)	4.3±0.58	4.9±0.85[a]	5.6±1.0[a,b]	<0.001
LVIDS (cm)	2.6±0.28	3.6±0.66[a]	4.7±0.91[a,b]	<0.001
RWT	0.50±0.13	0.60±0.24[a,c]	0.41±0.12	<0.001
LVM (g)	233.5±31.4	334.6±105.9[a]	403.8±134[a,b]	<0.0001
LVM/HT (g/m)	137.1±53.5	200.3±65.7[a]	237.1±89.3[a]	<0.0001
LVM/HT^2 (g/m^2)	82.7±32.2	121.0±39.9	142.7±53.7[a,b]	<0.0001
LVM/T$^{2.7}$ (g/m$^{2.7}$)	58.2±22.8	85.1±28.4[a]	102.2±37.7[a,b]	<0.001
LVM/BSA (g/m^2)	122.4±46.0	185.5±60.1[a]	219.3±81.9[a]	<0.001
FS (%)	41.0±5.9[b,c]	26.0±2.7	17.3±3.6	<0.001
LVEF (%)	76.7±10.2[b,c]	48.5±4.0	31.1±7.0	<0.001
E/e′	3.5±0.9	4.3±1.8[a]	5.2±2.6[a,b]	<0.001

Abbreviations: BSA, body surface area; *E*, early diastolic filling using transmitral flow; *e′*, early diastolic filling using tissue Doppler imaging; ECG, electrocardiography; FS, fractional shortening; HT, height; IVSTd, interventricular septal thickness at end diastole; LAA, left atrial area; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVIDD, left ventricular internal diameter in diastole; LVIDS, left ventricular internal diameter in systole; LVM, left ventricular mass; NS, nonsignificant; PWTd, posterior wall thickness at end diastole; RVD, right ventricular diameter in diastole; RWT, relative wall thickness.
[a]Significantly higher compared to subjects to normal LV systolic function.
[b]Significantly higher compared to subjects with mild LV systolic dysfunction.
[c]Significantly higher compared to subjects with severe systolic dysfunction.

Table 3. Comparison of echocardiographic parameters in male and female subjects

Variable	Male (N = 953)	Female (N = 994)	*P* value
RVD (cm)	3.14 ± 0.38	2.82 ± 0.33	<0.0001
Aortic diameter (cm)	2.19 ± 0.26	2.04 ± 0.22	<0.0001
LAD (cm)	3.60 ± 0.71	3.50 ± 0.59	<0.0001
IVSTd (cm)	1.14 ± 0.24	1.10 ± 0.54	<0.0001
PWTd (cm)	1.10 ± 0.35	1.03 ± 0.53	0.002
LVIDD (cm)	4.48 ± 0.66	4.26 ± 0.61	<0.0001
LVIDS (cm)	2.71 ± 0.68	2.69 ± 0.58	0.93
RWT	0.50 ± 0.18	0.50 ± 0.29	0.74
LVM/BSA (g/m²)	135.1 ± 48.1	119.5 ± 52.9	<0.0001
Fractional shortening (%)	35.0 ± 7.5	40.7 ± 7.0	<0.0001
Ejection fraction (%)	72.9 ± 13.6	76.0 ± 12.7	<0.0001

Abbreviations: BSA, body surface area; FS, fractional shortening; IVSTd, interventricular septal thickness diameter in diastole; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVIDD, left internal diameter in diastole; LVIDS, left ventricular diameter in systole; LVM, left ventricular mass; PWTd, posterior wall thickness at end diastole; RVD, right ventricular diameter in diastole.

dysfunction in a population of asymptomatic hypertensive black subjects. In this study, 6.7% of subjects had LV systolic dysfunction. The prevalence of 6.7% is less than 14% reported by Devereux *et al.*[11] in a mixed population of 2,086 asymptomatic black and white hypertensive subjects using the same cutoff values for LV systolic function that we used in our study and higher than the 4.7% and 3.7% prevalence reported, respectively, in the Copenhagen[17] and Rotterdam[18] Heart studies in unselected community cohort. The higher prevalence of LV systolic dysfunction in the study by Devereux *et al.* can be partly attributed to the inclusion of subjects with ischemic heart disease. We undertook stringent phenotyping in our study and excluded subjects with clinical features of coronary artery disease, given that it is well known that ischemic heart disease is an independent predictor of LV systolic dysfunction.[19] On the other hand, the Copenhagen[17] and Rotterdam[18] studies involved both unselected community cohorts rather than just hypertensive patients and also used lower cut-points to define LV systolic dysfunction, thereby accounting for the lower prevalence of LV systolic dysfunction in these studies compared to our study.

Similar to previous reports,[20,21] we found that our male subjects had worse LV systolic function compared to the female subjects. Our male subjects also had significantly greater LV chamber dilatation compared to the female subjects, similar to Heart of Soweto Study.[10] The explanation for this gender difference is uncertain, but it is generally known that cardiovascular disease tends to occur earlier in men than women.[22] This may explain the increased cumulative incidence of heart failure due to reduced LV ejection fraction in men compared with women in the Framingham cohort, which was associated with a higher cumulative incidence of myocardial infarction.[23] However, we observed that men had a lower LV ejection fraction compared with women despite actively excluding patients with either clinical or subclinical evidence of ischemic heart disease.[24,25]

Table 4. Multivariate analysis of independent covariates associated with left ventricular ejection fraction

Parameters	Standardized coefficient β	*P* value
Age	−3.07	0.002
Male sex	−2.61	0.011
Body mass index	−5.87	<0.0001
Diastolic blood pressure	−4.46	<0.0001
Diabetes mellitus	−2.56	0.013
Left atrial diameter	−2.51	0.012
Left atrial area	−2.71	0.008
Left ventricular diameter in diastole	−12.07	<0.0001
Posterior wall thickness in diastole	−3.24	<0.001
Left ventricular mass	−2.97	0.003
Left ventricular mass indexed for body surface area	−8.15	<0.0001

When diabetic and nondiabetic subjects were compared, the diabetic subjects had a lower LV ejection fraction compared to nondiabetic subjects, similar to previous findings.[11] This is not surprising as diabetes mellitus is an established independent risk factor for LV systolic dysfunction in hypertension.[26]

In regression analysis, lower LV ejection fraction as a continuous variable was associated with diastolic blood pressure. The relationship between blood pressure and LV systolic dysfunction in hypertension has been previously reported in the general population.[20] Furthermore, we observed a lower pulse pressure in patients with severe LV systolic dysfunction compared to those with mild LV systolic dysfunction and normal LV systolic function. This is partly attributable to a lower stroke volume, which is a contributor to increased arterial pulse pressure.[27,28] The relatively young age of our subjects can also partly explain the significantly higher pulse

pressure in subjects with severe LV systolic dysfunction as arterial pulse pressure has been found to be positively correlated with stroke volume in young patients.[29] Body mass index was also associated with a lower LV ejection fraction, as previously reported by Devereux *et al.*[11] Other factors that were independently associated with LV systolic dysfunction in our study included left atrial diameter, left atrial area, and higher LV mass index for height or body surface area. The relationship between left atrial size and LV systolic dysfunction has been linked to abnormal LV diastolic function, as left atrial size is a surrogate marker of raised LV filling pressure.[30,31] In addition, we found subjects with severe LV systolic dysfunction to have the worst diastolic function using E/e' followed by those with mild LV systolic dysfunction, thereby supporting the findings of Ballo *et al.*,[32] which showed that in asymptomatic hypertensive subjects, LV diastolic performance is associated with longitudinal systolic dysfunction.

Clinical implication

LV systolic dysfunction was present in 6.7% of our asymptomatic cohort of patients with hypertension presenting for the first time without any clinical features of coronary artery disease. Therefore, echocardiography should be performed in hypertensive subjects even when asymptomatic to identify LV systolic dysfunction. This may allow early treatment of LV systolic dysfunction to reduce the risk of heart failure and improve long-term survival, given that it has been shown that angiotensin converting enzyme inhibitors can not only delay the progression to symptomatic heart failure but can also prevent it.[33]

Limitation

Since the diagnosis of ischemic heart disease was made clinically using history, troponin I, electrocardiography, and echocardiography, with no myocardial perfusion imaging or coronary angiography, it is possible that subclinical coronary artery disease might have been missed. However, with the low prevalence of clinical myocardial infarction and the high cost of myocardial perfusion and coronary imaging in this environment, we did not think that it was justifiable for these subjects to have these investigations. Instead, we undertook careful and extensive phenotyping of our study population with respect to clinical, biochemical, electrocardiographic, and echocardiographic evaluation, which is a major strength of our study. This allowed us to exclude subjects with probable coronary artery disease to minimize its confounding effect on LV systolic function.

CONCLUSION

In an asymptomatic hypertensive cohort with no clinical evidence of ischemic heart disease in a population with a low prevalence of other cardiovascular risk factors, we identified LV systolic dysfunction in 6.7% of subjects. Therefore, echocardiography should be part of the routine evaluation of hypertensive patients to allow early detection and management of LV systolic dysfunction.

DISCLOSURE

The authors declared no conflict of interest.

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