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Relationship between hypertensive retinopathy and left ventricular diastolic function and geometry among hypertensive patients in a Nigerian Tertiary Hospital

[1] AA Onua, [2] CE Nwafor, [3] AC Mankwe
[1] Department of Surgery, University of Port Harcourt, Nigeria
[2, 3] Department of Medicine, University of Port Harcourt, Nigeria

Abstract
Background: Hypertensive retinopathy is recognized target organ damage among the poorly controlled hypertensives. Often than not, these patients simultaneously develop cardiovascular, cerebrovascular and renal complications preceded by the occurrence of subclinical left ventricular hypertrophy (LVH).
Aim: To determine the relationship between hypertensive retinopathy and left ventricular diastolic function and geometry among hypertensive patients attending University of Port Harcourt Teaching Hospital.
Materials and Methods: A longitudinal observational study of 175 consecutive hypertensive patients who were referred from the Cardiology unit to the Ophthalmology Department for ocular evaluation. Ophthalmological examinations were performed, which included ocular fundus assessment with direct ophthalmoscopy. Hypertension was classified according to the European Society of Hypertension/European Society of Cardiology guidelines. Two- Dimensional and Doppler echocardiographic examinations of the left ventricle were performed using ALOKA 2 Dimensional/Doppler and Color flow ultrasound machine, equipped with a 3.2 MHz transducer. Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 20.0
Results: One hundred and seventy-five patients were studied. Various degrees of hypertensive retinopathy and Left ventricular diastolic dysfunction depended on the duration of hypertension. The differences in the duration of hypertension and the abnormal fundoscopic findings was statistically significant (p=0.012). The differences in the duration of hypertension and the abnormal LV diastolic dysfunction was statistically significant (p=0.018).
Conclusion: There was a positive linear relationship between hypertensive retinopathy and Left ventricular diastolic dysfunction. Dilated fundoscopy could be used as a gold standard in the evaluation of left ventricular dysfunction among the hypertensives especially in a poor-resource setting.

Keywords: hypertensive retinopathy, left ventricular dysfunction, relationship

Introduction

Hypertension is among the leading causes of disabilities and deaths from non-communicable diseases (NCDs) in Africa [1, 2]. Public health response from the governments of many African nations still remains low, as available evidences show that a large number of hypertensive individuals are currently unaware of their condition [3].

The chances of development of complications affecting the cardiovascular and cerebrovascular systems, kidney and retina, often described as target-organ damage (TOD) increases with poor blood pressure control [4]. The development of major complications, which include stroke, congestive heart failure and myocardial infarction, renal failure and retinal vascular occlusion is often preceded by the occurrence of subclinical TOD, such as left ventricular hypertrophy (LVH), increased intima–media thickness of the large vessels, glomerular dysfunction, cognitive decline and hypertensive retinopathy [5, 6, 7].

Hypertensive retinopathy may be classified as mild (generalized or focal arteriolar narrowing, arteriovenous nipping, and increased arteriolar opacity), moderate (retinal microaneurysm or hemorrhage, cotton wool spot and hard exudates), and malignant (moderate retinopathy and optic disc swelling) depending on the strength of their associations with systemic vascular diseases [8]. Studies have shown that TOD increases cardiovascular risks over that already associated with elevated blood pressure alone. For example, it has been shown that once LVH has developed following long-standing systemic hypertension, it behaves as an independent risk factor and a predictor of both further cardiac complications [9] and other incident vascular events such as ischemic stroke and myocardial infarction [10]. In addition, hypertensive retinopathy has long been known as a predictor of systemic morbidity and mortality. Both epidemiological and clinical studies have provided evidence that markers of hypertensive retinopathy are associated with raised blood pressure, systemic vascular diseases, and subclinical cerebrovascular and cardiovascular disease, and predict incident clinical stroke, congestive heart failure and mortality due to cardiovascular complications [11]. This association of hypertensive retinopathy with other TOD has also been shown to be independent of blood pressure and other risk factors, which supports the recommendation that retinal vascular changes should be assessed in individuals with systemic hypertension for better extra-ocular TOD risk stratification [11]. While the number of reports on hypertensive TOD has been

on the rise on the African continent, the relationship between hypertensive retinopathy and other TOD such as Left Ventricular Hypertrophy (LVH) and left ventricular diastolic dysfunction has largely remained understudied.

This study therefore sets out to determine the relationship between hypertensive retinopathy and left ventricular diastolic function and geometry among hypertensive patients.

Materials and Methods

This was a longitudinal, observational study of 175 consecutive hypertensive patients who were referred from the Cardiology unit to the Ophthalmology Department of the University of Port Harcourt Teaching Hospital for ocular evaluation as part of a work-up of hypertensive patients. All participants provided informed consent and the study was approved by the ethical committee of University of Port Harcourt Teaching Hospital.

Inclusion criteria were established diagnosis of hypertension regardless of treatment regimen, duration and severity of hypertension, willingness to participate in the study. Exclusion criteria included inaccessibility of the fundus due to media opacities, and pregnancy.

All participants underwent blood pressure measurement with a mercury sphygmomanometer after the patient has been in a sitting position for five minutes, and body mass index (BMI) determination. They provided personal information about history of alcoholism, smoking, as well as family history of hypertension and stroke, and diabetes mellitus.

Routine ophthalmological examination was performed, which included measurement of visual acuity, slit-lamp examination of the anterior segment, intra-ocular pressure measurement with applanation tonometry, and dilated fundus assessment with direct ophthalmoscopy. Pupillary dilation was done with tropicamide 1% and phenylephrine 10%. The fundus examination specifically looked at retinal abnormalities consistent with hypertensive retinopathy, which was graded based on the Scheie classification [12]: Grade 0 = no visible change; Grade 1 = barely detectable arterial narrowing; Grade 2 = obvious arterial narrowing with focal irregularities; Grade 3 = grade 2 plus retinal haemorrhages, exudates, cotton wool spots, or retinal oedema; Grade 4: grade 3 plus papilloedema.

Hypertension was defined and classified according to the European Society of Hypertension/European Society of Cardiology guidelines [13]. Data about extra-ocular TOD such as LVH were recorded from cardiology medical records.

Echocardiography (Transthoracic)

M - Mode, 2 Dimensional and Doppler echocardiographic examinations of the left ventricle were performed with the subjects in the left lateral decubitus position, using ALOKA 2 Dimensional/Doppler and Color flow ultrasound machine, equipped with a 3.2 MHz transducer. All recordings and measurements were made using standard parasternal long axis and short axis views and apical 4-chamber views. Where necessary, an apical 2-chamber view was evaluated. Echocardiography was performed according to the recommendations of the American Society of Echocardiography (ASE) [14]. M-mode, interventricular septal thickness at end diastole (IVSd), the posterior wall thickness at end diastole (PWTd), the LV internal dimensions at end diastole (LVIDd) and at systole, and left atrial size at end systole were measured by use of a leading edge technique according to the guidelines of the ASE. End – diastolic LV wall thickness (LVWT) was calculated as (IVSd + PWTd), whereas relative wall thickness (RWT) was calculated as (IVSd + PWTd/LVIDd). Increased RWT was taken as RWT ≥ 0.45. LV systolic function was calculated by Teicholz's [15] formula. Presence of diastolic dysfunction was determined according to guidelines from the American Society of Echocardiography [16, 17, 18]. Left ventricular diastolic filling pattern was assessed by echocardiographic pulsed Doppler analysis. The diastolic mitral flow assessed by early diastolic peak flow velocity (E), the ratio of E to A (E/A) and the deceleration time of the early mitral velocity was recorded with the sample volume at the mitral leaflet tips. Deceleration time was measured as the time from peak E velocity to the time when the E wave descent intercepts the zero line. Isovolumic Relaxation Time (IVRT) was measured with a continuous wave Doppler beam intersecting left ventricular outflow and inflow tract [19]. Pulse Doppler recordings of trans mitral flow velocities were obtained between the tips of the mitral leaflets for measuring peak early left ventricular filling velocity/peak atrial filling velocity (E/A) and deceleration time(EDT). Valsalva maneuver was performed when applicable. Three consecutive cardiac cycles were assessed and averaged for Doppler measurements [20].

Filling Patterns in evaluated patients were classified as:

A. Normal Filling Pattern: normal myocardial relaxation [21]
B. Diastolic Dysfunction [22]
    1. STAGE I (MILD DYSFUNCTION): Defined as impaired relaxation with normal filling pressure.
    2. STAGE II (MODERATE DYSFUNCTION): Defined as pseudo normal filling pattern
    3. STAGE III (SEVERE REVERSIBLE DYSFUNCTION): Defined as a restrictive filling pattern and evidence of reversibility with valsalva maneuver; and
    4. STAGE IV (SEVERE IRREVERSIBLE DYSFUNCTION): Defined as a restrictive filling pattern without reversibility with valsalva [23].

The left ventricular mass index (LVMI) and left ventricular geometry were determined by m- mode and 2-dimensional echocardiography. Left ventricular mass was indexed to body surface area [24]. The LV mass was calculated using the American Society of Echocardiography formula modified by Devereux [25] as follows:

LVM (g) = $0.8 \times [1.04(LVIDd + LVPWd + IVSd)^3 - LVIDd^3] + 0.6$. LVH was considered to be present when LVMI exceeds $110 g/m^2$ for female and $134 g/m^2$ for male. The LV geometry were classified based on the evaluations of LVMI and RWT as follows:

A. Normal Geometry: Normal LVMI and RWT
B. Concentric Remodeling: Normal LVMI and Increased RWT.
C. Eccentric Hypertrophy: Increased LVMI and RWT<0.45
D. Concentric Hypertrophy: Increased LVMI and RWT ≥0.45.

Statistical Analysis

All data were analyzed using the commercially available statistical package for social sciences (SPSS) version 20.0

analytic software. Data were expressed as mean ± standard deviation. Student's t-test was used to compare means between groups. The proportion of patients with hypertensive retinopathy was compared among those with and without LVH using the Pearson chi-square test. The chi-square test was also used to compare the proportions of patients with TOD between those with and without hypertensive retinopathy. Multiple logistic regression analysis allowed assessment of the association of left ventricular systolic dysfunction and LVH with the likelihood of having hypertensive retinopathy. A $p< 0.05$ was considered statistically significant.

Results

Table 1: Age and Sex Distribution of the Participants

Age Group (Years)	Gender of Participants		Total (%)
	Male (%)	Female (%)	
35-40	5 (2.9)	6 (3.4)	11 (6.3)
41-45	0 (-)	5 (2.9)	5 (2.9)
46-50	0 (-)	19 (10.9)	19 (10.9)
51-55	30 (17.1)	10 (5.7)	40 (22.8)
56-60	17 (9.7)	24 (13.7)	41 (23.4)
61-70	5 (2.9)	17 (9.7)	22 (12.6)
71-75	13 (7.4)	14 (8.0)	27 (15.4)
76-85	10 (5.7)	0 (-)	10 (5.7)
Total	80 (45.7)	95 (54.3)	175 (100)
Pearson Chi Square Value=50.957 p-value =0.000			

One hundred and seventy-five persons participated in this study, 80 (45.7%) were male and 95 (54.3%) were female, with a mean age of 58.5 ± 12.3 years (range: 35–85). The difference between the male and female participants in this study was statistically significant (p=0.000) (Table 1).

Table 2: Duration of Hypertension and Fundoscopic findings in the study population

Duration of Hypertension (Years)	Fundoscopic Finding					Total (%)
	Normal (%)	Hypertensive Retinopathy Grade1 (%)	Hypertensive Retinopathy Grade2 (%)	Hypertensive Retinopathy Grade3 (%)	Hypertensive Retinopathy Grade4 (%)	
1-5	26 (14.9)	9 (5.2)	6 (3.4)	1 (0.6)	3 (1.7)	45 (25.8)
6-10	16 (9.1)	7 (4.0)	7 (4.0)	4 (2.3)	2 (1.1)	36 (20.5)
11-15	4 (2.3)	3 (1.7)	10 (5.7)	5 (2.8)	1 (0.6)	23 (13.1)
16-20	- (-)	- (-)	43 (24.6)	6 (3.4)	- (-)	49 (28.0)
21 & Above	- (-)	- (-)	8 (4.6)	14 (8.0)	- (-)	22 (12.6)
Total	46 (26.3)	19 (10.9)	74 (42.3)	30 (17.1)	6 (3.4)	175(100)
Pearson Chi Square=12.917; p=0.012; dF=4						

The differences in the duration of hypertension and the abnormal fundoscopic findings among the hypertensives in this study was statistically significant (p=0.012). (Table 2)

Table 3: Duration of Hypertension and Echocardiographic Findings of Diastolic Dysfunction in the Study Population

Duration of Hypertension (Years)	Echocardiographic Finding of Diastolic Dysfunction					Total (%)
	Normal Diastolic function (%)	Mild Diastolic Dysfunction (%)	Moderate Diastolic Dysfunction (%)	Severe Diastolic Dysfunction (Reversible) (%)	Severe Diastolic Dysfunction (Irreversible (%)	
1-5	32 (18.3)	8 (4.6)	5 (2.9)	- (-)	- (-)	45 (25.8)
6-10	10 (5.7)	17 (9.7)	7 (4.0)	2 (1.1)	- (-)	36 (20.5)
11-15	2 (1.1)	8 (4.6)	6 (3.4)	4 (2.3)	3 (1.7)	23 (13.1)
16-20	- (-)	2 (1.1)	18 (10.4)	20 (11.4)	9 (5.1)	49 (28.0)
21 & Above	- (-)	- (-)	5 (2.9)	6 (3.4)	11 (6.3)	22 (12.6)
Total	44 (25.1)	35 (20)	41 (23.6)	32 (18.2)	23 (13.1)	175(100)
Pearson Chi Square=11.946; p=0.018; dF=4						

The differences in the duration of hypertension and the abnormal LV diastolic dysfunction among the hypertensive in this study was statistically significant (p=0.018) (Table 3).

Table 4: Duration of Hypertension and Echocardiographic Findings of Abnormal Geometry in the Study Population

Duration of Hypertension (Years)	Echocardiographic Findings				
	Normal Geometry (%)	Concentric remodeling (%)	Eccentric hypertrophy (%)	Concentric hypertrophy (%)	Total (%)
1-5	40 (22.9)	5 (2.9)	- (-)	- (-)	45 (25.8)
6-10	27 (15.4)	7 (4.0)	-(-)	2 (1.1)	36 (20.5)
11-15	10 (5.7)	6 (3.4)	3 (1.7)	4 (2.3)	23 (13.1)
16-20	2 (1.1)	19 (10.9)	11 (6.3)	17 (9.7)	49 (28.0)
21 & Above	- (-)	5 (2.9)	8 (4.6)	9 (5.1)	22 (12.6)
Total	79 (45.1)	42 (24.0)	22 (12.6)	32 (18.2)	175(100)

The prevalence of abnormal geometry in the study population was 54.8%. The differences in the duration of hypertension and the abnormal LV geometry among the hypertensive in this study was statistically significant (p=0.018) (Table 4).

Correlation of Hypertensive Retinopathy Grading with Echocardiographic Findings

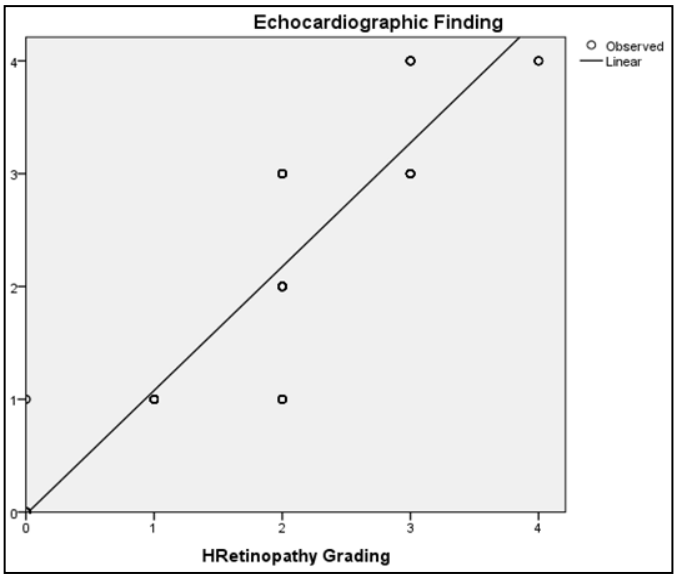

Fig 1: Relationship between the findings of hypertensive retinopathy and echocardiographic findings in the study population

There was a strongly positive linear relationship between the findings of hypertensive retinopathy and echocardiographic findings in the study population. This was statistically significant (p-value=0.000). (Figure 1).

Discussion

In this study, the modal age group of hypertensives was 56-60 years with a mean age of 57.9 ± 13.2 years. This is in keeping with the fact that advancing age is a non-modifiable risk factor for hypertension. Females were commoner than males in this study. It has been documented that men are at greater risk of heart disease than pre-menopausal women; however, post-menopausal women stands the same risk of hypertension as men [26, 27].

The prevalence of hypertensive retinopathy (HR) was 73.7%. The prevalence of HR was noted among patients with duration of hypertension of 16-20 years (28.0%) increasing thereafter up to 40.6% with those who had hypertension for 21 years and above (table 2). This trend shows that prevalence of hypertensive retinopathy increases with duration of hypertension. This was statistically significant (p=0.012). In Cuspidi *et al*, study in 2001 on 800 hypertensive patients, the prevalence of Grades 1 and 2 hypertensive retinopathy among hypertensive patients were 46% and 32%, respectively, and < 2% showed Grades 3 and 4 abnormalities [44]. In our study, the prevalence of Grades 1 and 2 retinopathy was 10.9% and 42.3%, respectively, which disagrees with Cuspidi *et al*, report only in those with Grade 1 retinopathy. However, in our study, the frequency of patients who had Grades 3 and 4 HR was less than those with Grades 1 and 2. This difference could be due to the abnormal LV geometry in patients with longer duration of hypertension and more advanced age compared to Cuspidi *et al*, study population. It is therefore logical to expect higher grades of HR to be more prevalent among our study population.

Also, our study shows that there was statistically significant higher number of hypertensive retinopathy patients with left ventricular diastolic dysfunction. This status was associated with duration of hypertension.

In Shirafkan *et al*, study, 92.1% of hypertensive patients were affected by hypertensive retinopathy [42] compared to 73.7% of patients in our study. This similarity between the two studies was most likely because both subjects were those who had LVH. This evidence could be indirectly indicative of an increased prevalence of retinopathy in hypertensive patients who suffer from LVH [42].

In Dahlöf *et al*, study, a positive correlation between the vascular involvement of the retina in the untreated hypertensive patients and left ventricular wall thickness on echocardiography was reported [43]. This study was in agreement with the results of our study, which showed a significant relationship between abnormal LV geometry and retinopathy.

There was a strongly positive linear relationship between the findings of hypertensive retinopathy and echocardiographic findings of diastolic dysfunction in this study which was statistically significant (p-value=0.000).

The prevalence of diastolic dysfunction assessed by reversed E/A ratio, deceleration time and isovolumic relaxation time (IVRT) in the participants in this study was 74.9.0%. Our finding compares well with those of Kingue *et al* in Cameroon where the prevalence of diastolic dysfunction was 67% [23] and Ike *et al* in their study on the relationship between diastolic dysfunction and the level of blood pressure in Blacks where a prevalence of 82.86% was observed [30].

The result of our study shows that the impaired relaxation pattern was found in less than one third (20.0%) of the hypertensives with diastolic dysfunction. This could be

explained by the fact that the participants in this study had longer duration of hypertension and more advancing ages which are important contributors to more severe abnormal geometry with resultant impaired relaxation of the left ventricle.

It was observed in our study that most of the hypertensives with diastolic dysfunction were mostly hypertensives with abnormal geometry (54.8%) with only 20.1% being hypertensives with normal geometry.

In this study, the pseudonormal pattern of diastolic dysfunction (moderate stage) was found in 23.6% of the hypertensives with diastolic dysfunction, most of whom were hypertensives with concentric remodeling of the left ventricle and a small proportion (2.4%) of them had normal geometry.

Severe diastolic dysfunction was seen in 31.3% of the hypertensives with diastolic dysfunction out of which 18.2% was reversible and 13.1% was irreversible. This could be explained by their longer duration of hypertension and older age.

The prevalence of abnormal geometry of the Left Ventricle in the participants of this study was 54.8%. Concentric remodeling was found in 24.0% of the cases while LVH constituted 30.8% of the prevalence of which 12.6% had eccentric hypertrophy and 18.2% had concentric hypertrophy. The grade of hypertensive retinopathy was related to age, duration of hypertension and abnormal left ventricular geometry.

Our study showed a positive correlation between hypertensive retinopathy and abnormal geometry and duration of hypertension. The is consistent with the report of Gee-Hee *et al* [45] in their work on the relation between Grade II hypertensive retinopathy and coronary artery disease in treated essential hypertensives that showed that the grade of hypertensive retinopathy was related to age, duration of hypertension, coronary artery disease (CAD), and left ventricular hypertrophy (LVH). Our investigation noted that the more severe and uncontrolled the BP and the longer the duration of hypertension, the more severe the abnormal geometry and the retinopathy. Additionally, the older the patient, the more severe the LVH was on echocardiographic analysis.

Conclusion

There was a strongly positive linear relationship between the findings of hypertensive retinopathy and echocardiographic findings in this study. Detailed dilated fundoscopy could be used as a gold standard in the evaluation of left ventricular dysfunction among the hypertensives especially in a poor-resource setting. The knowledge of the relationship between hypertensive retinopathy and left ventricular dysfunction could be a useful tool in the management of hypertensive patients.

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