WEST AFRICAN JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Left Ventricular Diastolic Function in a Predialysis Patient Population

La fonction ventriculaire gauche diastolique dans une population de patients prédialyse

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ABSTRACT

BACKGROUND: **Diastolic dysfunction is common in chronic kidney disease (CKD) accounting for 40%–66% of cardiovascular complications.**

OBJECTIVE: **To determine the prevalence of and factors associated with left ventricular diastolic dysfunction (LVDD) in adult Nigerians with CKD at presentation and to compare findings with those of hypertensive patients with normal renal function.**

METHODS: **Eighty-six consecutive patients with CKD were studied, comprising 43 hypertensives and 43 age- and sex-matched healthy subjects as controls. Clinical, laboratory, and echocardiographic variables were measured.**

RESULTS: **Left ventricular diastolic dysfunction was present in 62.8% of CKD patients, 79.1% of hypertensive patients and 25.6% of normal controls ($p < 0.001$. There was a positive correlation between left ventricular diastolic function (LVDF) and systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), severity of SBP, severity of DBP in CKD patients but not in hypertensive patients. There was a negative correlation between LVDF and age in CKD patients and hypertensive patients. Linear multiple regression analysis showed age as the only predictor of LVDD.**

CONCLUSION: **There is a high prevalence of diastolic dysfunction in CKD patients at first presentation to a nephrologist in Nigeria. WAJM 2010; 29(4): 225–229.**

Keywords: **Left ventricular diastolic dysfunction, chronic kidney disease, predialysis, echocardiography, Nigeria.**

RÉSUMÉ

CONTEXTE: La dysfonction diastolique est commun dans la maladie rénale chronique (IRC), qui représentent 40%–66% de complications cardiovasculaires.

OBJECTIF: Déterminer la prévalence et les facteurs associés à une dysfonction diastolique ventriculaire gauche (LvDD) dans les Nigérians adultes souffrant d'IRC à la présentation et de comparer les résultats avec ceux des patients hypertendus avec une fonction rénale normale.

METHODES: Quatre-vingt-six patients consécutifs atteints d'IRC ont été étudiés, composé de 43 hypertendus et 43 à l'âge et le sexe des sujets sains appariés comme témoins. Cliniques, de laboratoire, et les variables échocardiographiques ont été mesurés.

RÉSULTATS: dysfonction ventriculaire gauche diastolique était présent dans 62,8% des patients atteints d'IRC, 79,1% des patients hypertendus et 25,6% des témoins normaux ($p < 0,001$. Il y avait une corrélation positive entre la fonction diastolique du ventricule gauche (LVDF) et la pression artérielle systolique (PAS), la pression artérielle diastolique (PAD), la pression artérielle moyenne (MAP), la gravité de la SBP, de la gravité de la DBP chez les patients IRC, mais pas chez les patients hypertendus. Il y avait une corrélation négative entre l'âge et LVDF chez les patients IRC et les patients hypertendus. linéaire multiple Une analyse de régression a montré que l'âge le seul facteur prédictif de LvDD.

CONCLUSION: Il existe une forte prévalence de la dysfonction diastolique chez les patients CKD à première présentation à un néphrologue au Nigeria. WAJM 2010; 29 (4): 225–229.

Mots-clés: dysfonction ventriculaire gauche diastolique, la maladie rénale chronique, en attente de dialyse, l'échocardiographie, au Nigeria.

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Abbreviations: a, peak late/atrial diastolic filling velocity; BMI, Body Mass Index; **CGN,** Chronic Glomerulonephritis; **CHF,** Congestive Heart Failure; **CKD,** Chronic Kidney Disease; **e, peak early diastolic filling velocity; eGFR,** estimated Glomerular Filtration Rate; **HTN,** Hypertension; **LV,** Left Ventricle; **LVDD,** Left Ventricular Diastolic Dysfunction; **LVDF,** Left Ventricular Diastolic Function; **LVH,** Left Ventricular Hypertrophy; **LVMI,** Left Ventricular Mass Index; **NKFQOI,** National Kidney Foundation Quality Outcome Initiative; **SBP,** Systolic Blood Pressure.

INTRODUCTION

Various forms of cardiac abnormalities occur in patients with chronic kidney disease (CKD). The prevalence of cardiac dysfunction is high in CKD patients at initiation of dialysis primarily because CKD is associated with dual volume and pressure overload leading to eccentric and / or concentric hypertrophy.[1]

Hypertension which is present in most patients with CKD as well as some medications that cause sodium and water retention also contributes to the alteration of diastolic function. Left ventricular diastolic dysfunction is noted to be the cause of congestive heart failure (CHF) in half of these patients at the beginning of dialysis.[2] Presence of CHF at initiation of dialysis is an important predictor of cardiovascular and overall mortality in a dialysis population.[2] In a non-CKD population left ventricular diastolic dysfunction mainly affects elderly or hypertensive patients.[1]

CKD patients constitute 2–8% of all hospital admissions in Nigeria.[3] Although cardiovascular complications are common in them, there is paucity of information on LV diastolic dysfunction in African black CKD patients. Hypertension is common in our patients with CKD with prevalence as high as 85%.[4] It is the single most important factor in the progression of renal failure. LV diastolic dysfunction has been documented as an early marker of the pathological effects of hypertension on the heart.[5, 6]

Left Ventricular Diastolic Dysfunction occurs in patients with advanced CKD who are already on dialysis. It is not known when this abnormality starts in CKD patients. There is paucity of data on presence of LVDD in CKD patients yet to commence dialysis in our environment. This study was designed to answer the question: Is LVDD common in predialysis CKD patients in Nigeria and to what extent?'

SUBJECTS, MATERIALS, AND METHODS

Study Site

This study was a cross sectional, comparative, study conducted at the University of Nigeria Teaching Hospital (UNTH), Enugu, Nigeria from January 2002 to December 2003. The hospital serves approximately 25–30% of the Nigerian population estimated to be 129 million[7] at the time of study.

The study was approved by the hospital's Ethics Committee and informed consent obtained from the participants.

Study Population

The study group was drawn from patients attending the medical outpatient and renal clinics of the hospital. One hundred consecutive patients with CKD who satisfied the inclusion criteria were evaluated. Eighty-six patients completed the study. Forty-three sex-matched hypertensive patients with normal renal function were selected. Forty-three age and sex-matched subjects were also selected as controls.

Patients of both sexes fifteen years and above, with established chronic kidney disease i.e. patients with symptoms and signs of renal disease ≥ 3 months and who had laboratory (proteinuria>1g/dl) or imaging (kidney sizes <9cm length) and who had GFR < 60ml/min/1.73m^2 and who had not received any form of renal replacement therapy and were presenting for the first time were included in the study. Hypertensive patients with normal renal function, who had no evidence of cardiac failure were also included.

The following patients were excluded from the study: patients younger than 15 years, and patients with acute kidney injury. Other exclusion criteria were history and clinical features consistent with primary cardiovascular disease (cardiomyopathy, valvular heart disease, pericardial disease) and patients on dialysis and kidney transplant patients.

Control subjects consisted of normal subjects attending the hospital for medical examination for employment, pre-marital evaluation and hospital staff. Individuals with known cardiac, renal, respiratory and hepatic diseases were excluded. No participant in this study abused drugs or alcohol.

Anthropometric data comprising height (Ht) and weight (Wt) were obtained from the study participants using a standiometer. The body mass index (BMI) was calculated from data using the formula: BMI= Ht/Wt^2 where height was in meters and weight in kilograms. Systolic and diastolic blood pressures (SBP and DBP respectively) were measured with Accoson's® mercury sphygmomanometer. The blood pressure of CKD patients, control and hypertensive subjects were taken in sitting position from the right arm after 15 minutes rest. The mean of three values 10 minutes apart was taken.

Definitions: Hypertension was defined as mean arterial pressure ≥ 105 mmHg and/or SBP ≥ 140mmHg and/or DBP (using fifth korotkoff phase) ≥ 90mmHg.[8] Anaemia was defined as per WHO, ie Haemoglobin level < 12g/dl for female subjects and < 13g/dl for male subjects were considered anaemic.

Other measurements

Serum albumin, calcium and phosphate levels were measured and documented. Serum calcium levels were corrected in relation to the albumin with the formula 0.01 mmol/l added to the serum calcium concentration for every 4g/l that albumin was < 40g/l; for albumin levels >40g/l, 0.01 mmol/l was subtracted.[9]

Creatinine clearance was estimated using the Cockcroft and Gault equation,[10] which has been found to correlate closely with measured creatinine clearance in Nigerians.[11] Degree of renal impairment was classified using the National Kidney Foundation Quality Outcome Initiative (NKFQOI) classification.[12]

Each participant underwent m-mode, two-dimensional and Doppler echocardiography, with a Siemens Sonoline CD echocardiographic machine, equipped with a 3.5 MHz transducer, a video recorder and print out processor. For assessment of left ventricular (LV) diastolic function, a pulsed Doppler of the LV inflow was performed in the apical 4-chamber view. The mitral valve was interrogated from the apical four chamber view with the pulsed wave dopplar sample volume positioned just into the left ventricle, immediately distal to the tips of the mitral valve leaflets. The position of the sample volume was adjusted until the highest peaks of diastolic flow velocity with optimal graphic waveforms

were obtained.[13] A well defined biphasic diastolic flow would be seen, with a rapid upstroke in early diastole to a peak (E) followed by a fall in velocity, and velocity increasing again to a peak (A) after atrial systole, and then decreasing. Echocardiograms were recorded on video and thermal paper for later analysis. All measurements were performed separately on three cardiac cycles and the average recorded. Two cardiologists and echocardiographers recorded and read the echocardiograms to reduce intra-observer bias. Left ventricular diastolic dysfunction was defined as an E/A ratio of <1.2 (E stands for Doppler peak early diastolic filling velocity and A, peak late/atrial diastolic filling velocity). Although many investigators use E/A ratio </ 1.0 as index of LVDD, we chose E/A < 1.2 for ease of comparison with similar studies[14]. The echocardiographic studies were done free to patients and the cost underwritten by the hospital management to encourage research.

Statistical Analysis

The statistical package for social sciences (SPSS Inc., Chicago IL) version 11.5 statistical software was used for data analysis. For continuous variables, mean values and standard deviations were calculated, and the means compared using analysis of variance. Categorical variables were compared using the nonparametric test chi-square. All tests were two-tailed, and $p < 0.05$ taken to be statistically significant.

Pearson's and Spearman Rho correlation were used to assess the relationship between E/A ratio and the variables (Age, Sex, SBP, DBP, MAP, severity of SBP, severity of DBP, HTN duration, estimated glomerular filtration rate (eGFR), Calcium, and Left ventricular mass index-LVMI) as appropriate. Significant variables were further analyzed using the linear regression analysis to determine variables that could predict LVDD in CKD patients.

RESULTS

Study Characteristics

One hundred patients were recruited and 86 completed the study. Fourteen patients dropped out because of: incomplete results, ten, lost to follow up, three; and withdrawal of consent, one. Forty-three sex-matched hypertensive subjects and forty-three age. and sex-matched normal controls were also recruited into the study. The characteristics of the study population are shown in Table 1. The SBP, DBP and MAP of the CKD patients and hypertensive patients were significantly higher than those of the control subjects, $p < 0.001$. All the CKD patients belonged to either stage 4 (17.9%) or stage 5 (82.1%), The rest of the study characteristics are as shown in the table.

Prevalence of LVDD in the Study Population

There were 54(62.8%) patients with LVDD in predialysis CKD patients. The prevalence rate of LVDD in hypertensive patients without kidney disease was 79.1% and for control subjects 25.6%, (Table 2). There was statistically significant difference between the prevalence of LVDD in CKD and hypertensive patients on one hand and control subjects on the other hand, $p < 0.001$.

Factors Associated with LVDD

The following factors: systolic blood pressure (SBP), $r = .384$, $p < 0.001$; diastolic blood pressure (DBP), $r = 281$, $p = 0.009$; mean arterial pressure (MAP), $r = .343$, $p = 0.001$; severity of SBP, $r = .234$, $p = 0.030$; and severity of DBP, $r = .233$, $p = 0.030$, correlated positively with LVDD in CKD patients but not in hypertensive patients, Table 3. There was a negative

Table 1: Characteristics of Study Participants

Characteristic	CKD patients	HTN patients	Control subjects	F	P-value
N	**86**	**43**	**43**		
Age (years)	41.91±15.40	48.16±9.54	41.44±15.47	3.31	0.039
BMI (kg/m^2)	24.54±4.74	28.11±4.89	26.91±5.02	8.76	<0.001
SBP (mmHg)	172.09±32.47	165.91±23.43	117.23±9.31	66.10	<0.001
DBP (mmHg)	109.08±21.62	106.21±10.27	72.56±6.85	75.16	<0.001
MAP	129.91±24.23	126.11±12.64	87.02±6.87	81.13	<0.001
Hb (g/dl)	7.75±2.13	13.21±1.21	12.82±0.74	214.61	<0.001
eGFR (ml/min/1.73m^2)	9.71±5.55	82.26±18.08	99.60±9.25	1229.29	<0.001
Ca + PO_4 (mmol/L)	5.74±2.80	3.02±0.30	3.45±0.68	33.61	<0.001
Serum albumin (g/L)	31.05±6.71	46.53±5.99	44.47±6.95	103.60	<0.001

CKD, chronic kidney disease; HTN, hypertension; N, number of participants; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; Hb, haemoglobin concentration; eGFR, estimated glomerular filtration rate; Ca, calcium; PO_4, phosphate. Values are mean ±SD

Table 2: Echocardiographic Findings of Study Participants

Characteristic	CKD patients	Hypertensive patients	Control subjects	F	P-value
N	**86**	**43**	**43**		
LVMI (g/m^2)	215.02±79.72	153.68±60.39	85.08±23.44	52.32	<0.001
E (cm/s)	72.17±25.86	56.23±12.97	66.97±18.97	7.79	<0.001
A (cm/s)	69.78±20.14	63.28±14.06	50.89±14.47	16.77	<0.001
E/A Ratio	1.11±0.53	0.94±0.33	1.42±0.54	10.96	<0.001
E/A < 1.2, N (%)	54 (62.8)	34 (79.1)	11 (25.6)		<0.001

CKD, chronic kidney disease; N, number of participants; LVMI, left ventricular mass index; E, early diastolic filling volume; A, peak late/atrial diastolic filling volume.
Values are mean ± SD except E/A<1.2 in percentage.

Table 3: Correlationship between Early to Late Diastolic Filling Velocity Ratio (EAR) and other Variables among Study Participants

EAR v Variable	Chronic Kidney Disease N = 86		Hypertension N = 43		Control Subjects N = 43	
	r	p-value	r	p-value	r	p-value
Age (years)	–0.260	0.015	–0.301	0.050	–0.488	0.001
Male gender	0.182	0.094	0.112	0.475	–0.010	0.950
Female gender	–0.182	0.094	–0.112	0.475	0.010	0.950
SBP (mmHg)	–0.384	<0.001	–0.109	0.488	–0.163	0.297
DBP (mmHg)	0.281	0.009	0.148	0.343	–0.169	0.280
MAP	0.343	0.001	0.013	0.933	–0.167	0.285
Severity of SBP	0.234	0.030	0.081	0.603		
Severity of DBP	0.233	0.039	0.075	0.632		
Duration of HTN (yrs)	–0.103	0.346	–0.023	0.882		
LVMI (g/m^2)	–0.122	0.110	–0.247	0.110	0.067	0.668
eGFR (ml/min/1.73m^2)	–0.017	0.878	0.249	0.108	–0.093	0.554
Serum Ca^{2+} (mmol/L)	–0.138	0.208	0.065	0.677	–0.077	0.624

R, correlation coefficient; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HTN, hypertension; Yrs, years; LVMI, left ventricular mass index; eGFR, estimated glomerular filtration rate.

Table 4: Multiple Linear Regression Analysis of Factors that Correlate with Left Ventricular Diastolic Dysfunction in CKD Patients

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	SE	Beta	t	P
1	(Constant)	0.501	0.411		1.218	0.227
	age	–0.009	0.004	–0.276	–2.618	0.011
	systolic bp	0.005	0.011	0.309	0.472	0.638
	diastolic bp	–0.018	0.020	–0.743	–0.888	0.377
	mean arterial pressure	0.017	0.029	0.766	0.566	0.573
	classifcation of SBP	–0.076	0.153	–0.143	–0.497	0.620
	classification of DBP	0.058	0.152	0.116	0.384	0.702

Dependent Variable: E/A ratio

correlation between LVDD and age in CKD patients (r = –.260, p = 0.015) and control subjects (r = –.488, p = 0.001), Table 3. Linear multiple regression analysis showed age as the only predictor of LVDD in CKD patients, Table 4.

Comparison of LVDD in CKD and Hypertensive Patients

There was no statistical difference in the prevalence rates of LVDD between the CKD patients and hypertensive patients without kidney disease, p = 0.062. However when age and BMI were controlled for, this became significant (partial coefficient –0.761, p < 0.001).

DISCUSSION

The study demonstrated a high prevalence of LV diastolic dysfunction (62.8%) in our CKD patients at first presentation, before any form of renal replacement therapy began. Many studies have shown a prevalence of 40–66% regardless of treatment i.e. haemodialysis, peritoneal dialysis or even renal transplantation.[15,16,17] The prevalence of LVDD was higher in hypertensive patients without kidney disease compared to the CKD patients but this did not reach statistical significance, p = 0.062. However when age and BMI were controlled for this difference became significant, p < 0.001. This may be explained by the higher mean age (48.16 ±9.54 versus 41.91 ±15.40), p = 0.016, and higher mean BMI (28.11 ±4.89 versus 24.54 ±4.74), p < 0.001, of hypertensive patients relative to the CKD patients. It is worthy of note that our study demonstrated such a high prevalence of LVDD in CKD patients despite the fact that none of the patients has started dialytic therapy. Echocardiographic abnormalities of LV functions are recognized predictors of morbidity and mortality in dialysis and often present when dialysis treatment is initiated.[2] Diastolic dysfunction and the LV mass/volume ratio are associated with a greater incidence of intradialytic hypotension.[18,19] Studies have also related LV diastolic dysfunction to higher perioperative mortality from pulmonary oedema at the time of renal transplantation.[2] These patients therefore run a higher risk of sudden death especially during dialysis because of the changes in fluid balance. It is therefore important to recognize and correct these cardiac alterations and their risk factors early before commencement of dialysis. The situation is grim in Nigeria and many developing countries where patients present late to health facilities for several reasons related mainly to poverty, ignorance and poor financing of the health sector.

Age, sex, hypertension, anaemia and albuminuria are known cardiovascular risk factors in CKD and hypertensive patients. Of the variables tested, systolic blood pressure, diastolic blood pressure, mean arterial pressure, severity of SBP, and severity of DBP, correlated positively with LVDD in CKD patients but not in hypertensive patients, There was also negative correlation between LVDD and age in CKD patients and control subjects. Regression analysis showed age as the only predictor of LVDD in CKD patients. Left ventricular hypertrophy (LVH) is common in our patients and also present to some degree in normal subjects without hypertension or renal disease, as shown

in a previous study.[4] Diastolic dysfunction is usually associated with LVH, although the two may be dissociated.[2] This may explain the relatively high prevalence of LVDD in the control subjects in this study. All blood pressure indices (SBP, DBP, MAP, severity of hypertension and duration of hypertension) all correlated with LVDD in CKD patients. A previous study in this environment in hypertensive patients without renal disease documented a positive relationship between LV diastolic dysfunction and level of blood pressure.[19]

Limitations of the Study: This study has some limitations. Because few patients presented in early stages of CKD, the influence of early stages of CKD on LV diastolic function could not be assessed. A larger sample size which will include early stages of CKD may yield additional information.

Conclusion

This study has demonstrated a high prevalence of diastolic dysfunction in predialysis CKD patients (62.8%) in a developing country at first evaluation by a nephrologist. Also it has identified SBP, DBP, MAP, severity of hypertension and age as factors associated with LVDD in CKD patients with age being the best predictor of the condition. A statistically insignificant difference in the prevalence of LVDD between hypertensive patients and CKD patients was observed with the prevalence higher in the hypertensive patients. However, when age and BMI were controlled for, the observed difference became significant. It is of note that patients often present late in our environment and with complications. Unfortunately it is very costly to treat CKD/end stage renal disease, and most of our patients cannot afford adequate and appropriate treatment. There is no articulated health insurance program or social security system to help these patients in most developing countries like Nigeria. However, strategies and measures to prevent the development and progression of diastolic dysfunction at an early stage may prove more effective. Early detection and treatment of causes of CKD should be pursued aggressively at the primary prevention level.

ACKNOWLEDGEMENT

The authors are grateful to Dr. B. C. Anisiuba for his contributions in performing and reading the echocardiography.

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