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Letter to the Editor

Contributions of pulmonary hypertension to HIV-related cardiac dysfunction

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A B S T R A C T

Background/Aim: To evaluate the prevalence of pulmonary hypertension among patients living with HIV/AIDS and to determine its contribution to cardiac dysfunction.

Method: A hospital based cross sectional study was carried out over a 6-month period at the Jos University Teaching Hospital. The subjects were 200 confirmed HIV positive patients, ≥ 18 years of age who consented to the study. Physical examination, laboratory investigations, 2 dimensional and Doppler echocardiography were conducted on the subjects.

Results: The mean age of the patients was 38 ± 9 years, and there were 142 females (71%). Females were younger, mean age 36 ± 8 years versus 41 ± 10 years for males (p -value < 0.01). The median CD4 cell count was 312 cells/ μ l, there were no homosexual or intravenous drug user among the subjects.

Eight of the subjects had pulmonary hypertension, with a case prevalence of 4%, and this had no relationship to CD4 cell count. Both systolic and diastolic functions were worse in subjects with pulmonary hypertension, with a negative correlation between mean pulmonary arterial systolic pressure (mPASP) and parameters like ejection fraction ($r = -0.28$, p -value 0.0003), fractional shortening ($r = -0.21$, p -value 0.003), deceleration time ($r = -0.13$, p -value 0.09).

Conclusion: Immune-suppression affects the cardiac function adversely and coexisting pulmonary hypertension contributes to poor systolic and diastolic function in affected patients. The subtle nature of presentation of pulmonary hypertension and other cardiac dysfunctions in HIV/AIDS patients demand a high-index of suspicion and early intervention if detected, to ensure better care for these emerging threats to our patients.

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1. Introduction

Pulmonary hypertension is one of the causes of heart disease in HIV/AIDS and is an independent predictor of mortality in affected patients.^{1–3} The first case of pulmonary hypertension seen in HIV infected patient was described by Kim and Factor⁴ in 1987, subsequently the increasing report led to the inclusion of HIV associated pulmonary hypertension as a distinct entity in WHO classification at the 3rd world symposium held in Venice in 2003.²

Majority of investigations into pathogenesis of pulmonary arterial hypertension (PAH) have centered on dysfunction of the pulmonary vasculature with a primary focus on endothelial and vascular smooth muscle cells. However, the prevalence of autoimmunity, viral infections and chronic inflammation in association with certain form of PAH, has led some to propose

that vascular remodeling seen in PAH is secondary to immune dysfunction, and that chronic depletion of CD4 T cells could lead to a loss of T regulatory activity and unchecked humoral immunity.⁵ This later point has been corroborated by other workers, drawing the conclusion that conditions commonly associated with PAH, such as systemic sclerosis and HIV, are associated with abnormalities in CD4 T-cell function and exhibit a similarly inflamed pulmonary vascular pathology.^{6,7}

Pulmonary hypertension is observed in all groups of patients with HIV irrespective of the degree of immune-deficiency.⁸ In patients with HIV-related pulmonary hypertension (HRPH), the median survival [300 days with conventional therapy⁹] is decreased, and in most cases death is related to pulmonary hypertension.^{10,11}

Signs and symptoms of HIV related pulmonary hypertension are nonspecific, as a result of which diagnosis is often

delayed. This study was aimed at determining the prevalence of pulmonary hypertension among HIV infected patients at the Jos University Teaching Hospital (JUTH), North-central Nigeria and further evaluate the contribution of pulmonary hypertension to cardiac dysfunction.

2. Method

2.1. Study design

This was a hospital based cross sectional study involving 200 HIV-infected cohorts, carried out between May and November, 2010. Subjects were 18 years and above, consecutively recruited, and gave informed consent before commencement of the study. The following were excluded from the study; Patients with dyspnea of respiratory origin, patients with history of heart disease predating HIV infection, those with severe anaemia, and patients with Diabetes Mellitus. Also excluded were patients with a history of significant alcohol consumption, those with known connective tissue disease or sickle cell anaemia, and patients with peripartum cardiomyopathy.

2.2. Data collection

Subjects had questionnaire administered on them, based on which those that qualified had physical examination. They were categorized based on the NYHA questionnaire into those with dyspnea (NYHA I–IV), classified as NYHA-positive, and those without dyspnea as NYHA-negative. This was followed by laboratory workup for hemoglobin concentration, CD4 cell count, HIV viral load, serum lipid profile, Electrocardiogram, Hepatitis B surface antigen (HBsAg) and Anti-HCV antibody.

2.3. Echocardiography

All 200 patients underwent qualitative two dimensional transthoracic echocardiography, from which M-mode images were derived as well as Doppler flow examination with Aloka®-SSD4000 using a 3.5 MHz transducer. Left ventricular internal diameter (LVID) in systole and diastole, FS and EF were determined using standard protocol.¹² Using continuous wave Doppler, sampling of peak regurgitation jet velocity across tricuspid valve was used to estimate right ventricular to right atrial systolic pressure gradient, according to modified Bernoulli equation ($4 \times [\text{tricuspid regurgitation jet velocity}]^2$).¹³ $\text{RVSP} - \text{RAP} = 4\text{VTR}^2$, $\text{PASP} = 4\text{VTR}^2 + \text{RAP}$.

Pulmonary hypertension was defined by pulmonary arterial systolic pressure (PASP) ≥ 25 mmHg at rest. Cardiac dysfunction (HRCD) was defined based on echocardiographic findings as shown in Table 1, and subjects were either classed as having heart disease (if they had pulmonary hypertension or any other form of cardiac dysfunction) or without heart disease if their echocardiography was normal.

3. Statistical analysis

The data were analyzed with the Epi info version 3.5.3 (2011, CDC Atlanta Georgia). Continuous variables were expressed as

Table 1 – Clinical definitions used for patient classification.

Left ventricular systolic dysfunction	Fractional shortening <28% Ejection fraction <50% Without LV dilatation (LVIDD<55 mm)
Isolated left ventricular dilatation	LVIDD ≥ 55 mm with normal fractional shortening ($\geq 28\%$)
Dilated cardiomyopathy (DCM)	Ejection fraction <50% Fractional shortening <28% LVIDD > 55 mm, with global hypokinesia
Right ventricular dysfunction	RVIDD ≥ 30 mm or RVIDD $>$ LVIDD
Pulmonary hypertension	PASP ≥ 30 mmHg, and/or peak tricuspid regurgitation (VTR) > 2.5 m/s. Mild 30–40 mmHg Moderate 41–50 mmHg Severe > 50 mmHg
Diastolic dysfunction	Grade 1 E/A < 1.0 Deceleration time (DCT) > 220 ms IVRT > 92 ms (< 30 years), > 100 ms (30–50 years), > 105 ms (> 50 years) Grade 2 E/A 1–2 DCT 150–200 ms Grade 3 E/A > 2.0 DCT < 150 ms.

means $\pm$ standard deviation (SD). Differences between group means were tested by two-tailed student t-test. A Chi-square (χ^2) statistics was calculated to identify associations between categorical variables. Analysis of variance was used to compare mean echocardiography data where appropriate. p value < 0.05 was considered significant.

4. Results

4.1. General characteristics

The mean age of the study population was 39 years, with majority of the study population (89%) falling within the age range of 30–39 years and 26% being 50 years and above (Table 2). There were 142 females (71%) constituting the bulk of the patients, majority of the subjects were married and a lot more had at least secondary level of education, while a greater percentage of them were civil servants. Seventy seven percent (77%) of our subjects were not using alcohol.

There was no significant difference in occurrence of heart disease among the age groups, while significantly more males had heart disease compared to females (χ^2 8.69, p value 0.003). The other socio-demographic characteristic showed no significant difference in the two groups.

4.2. HIV-related pulmonary hypertension

The case prevalence of HIV-related pulmonary hypertension (HRPH) was 4.0%. There was no significant difference in the case prevalence of HRPH between females (6.9%) and males (2.8%) [$\chi^2 = 1.78$, p -value = 0.18].

There was no significant difference in the mean age of subjects with HRPH, 39 (9.3) years and those without HRPH, 38 (8.8) years; $p = 0.66$. The ratio of male to female was 1:1.

Table 2 – Socio-demographic characteristics of study population.

Characteristics	Frequency (n)	Percentage (%)	Heart disease n (%) n = 85	No heart disease n (%) n = 115
Age Groups (years)				
20–29	30	1.5	14 (16.5)	16 (13.9)
30–39	89	44.5	34 (40.0)	55 (47.8)
40–49	55	27.5	22 (25.9)	33 (28.7)
50 and above	26	13	15 (17.6)	11 (9.6)
Sex				
Female	142	71	34 (40)	24 (21)
Male	58	29	51 (60)	91 (79)
Marital status				
Divorced	7	3.5	2 (2.4)	5 (4.3)
Married	115	57.5	49 (57.6)	67 (58.3)
Separated	6	3	3 (3.5)	4 (3.5)
Single	24	12	11 (12.9)	12 (10.4)
Widowed	48	24	20 (23.5)	27 (23.3)
Education				
None	15	7.5	4 (4.7)	11 (9.6)
Informal	3	1.5	1 (1.2)	2 (1.7)
Primary	50	25	21 (24.7)	29 (25.2)
Secondary	74	37	33 (38.5)	42 (36.2)
Tertiary	58	29	26 (30.6)	31 (27)
Occupation				
Civil servant	59	29.5	25 (29.4)	33 (28.7)
Craft worker	28	14	11 (12.9)	17 (14.8)
Farmers	17	8.5	9 (10.6)	8 (7.0)
Housewife	30	15	18 (21.2)	13 (15.3)
Student/Applicant	17	8.5	9 (10.6)	8 (7.0)
Traders	49	24.5	13 (15.3)	36 (42.4)
Alcohol use				
Yes	46	23	20 (23.5)	26 (22.6)
No	154	77	65 (76.5)	77 (77.4)

Heart disease = Presence of HIV-related cardiac dysfunction (HRCDD) or HIV-related pulmonary hypertension (HRPH).

Table 3 compares the socio-demographic characteristics among subjects with HRPH; the student *t* test shows statistical significance in sex, educational status, alcohol use and NYHA classification. But when these variables were put in logistic regression model, only sex showed a trend (Table 4).

Neither the duration of HIV diagnosis (*p*-value = 0.27), nor the duration of Highly active anti-retroviral therapy (HAART) (*p*-value = 0.27), had any statistically significant relationship with the presence of HRPH.

The diagnosis of HRPH was made earlier (36 months) following HIV positive result than other types of HIV-related cardiac dysfunction (HRCDD) [41 months], though not significant (*p* = 0.27). Dyspnea as evaluated with NYHA showed significant difference between subjects with heart disease and those without ($X^2 = 5.07$, *p* = 0.02), while comparing with HRPH subjects, it was less significant ($X^2 = 11.5$, *p* = 0.07). Fifty percent of HRPH subjects were in NYHA III and IV, compared to 30.8% of subjects with other forms of HRCDD.

4.3. Pulmonary hypertension and left ventricular function

As seen in Table 5 and Fig. 1, mPASP showed negative correlation to some echocardiographic parameters. It was most evident with ejection fraction (EF) and fractional shortening (FS), *p* < 0.01, while deceleration time (DCT) was next with

p = 0.09. Another parameter noticed to have a negative correlation though with non-statistically significant *p*-value was left ventricular posterior wall in systole (LVPWS), *p* = 0.27. Subjects with pulmonary hypertension had dilated left ventricle, but showed a positive correlation with coefficient of correlation of 0.125, and *p* = 0.08.

5. Discussion

The case prevalence of HIV-related pulmonary hypertension (HRPH) in the study was 4.0%, which is close to the prevalence rates of 5.5% and 5% reported in the US¹⁴ and Africa.¹⁵ The female to male ratio of HRPH in the study was 1:1, we had more females in the study and they were older than the males, and older when compared with other females without HRPH. Other works have reported female to male ratios between 1.2 and 1.6:1.^{16–18} Males with HRPH in our study were younger than those without it, similar to the finding of a Swiss cohort study.¹⁹ This is contrary to the trend in Europe where HRPH presents at a younger age than those with other forms of pulmonary hypertension, and unlike idiopathic PAH, which is more common in women than in men [ratio of men to women 1:1.7]^{16,17} probably owing to early presentation. Aging and longevity are often associated with increase in systemic markers of inflammation, such markers include plasma

Table 3 – Comparing the socio-demographic parameters of subjects with HIV-related pulmonary hypertension and subjects with no heart disease.

Characteristics	Frequency (n)	Percentage (%)	No heart disease n (%) n = 115	HRPHT n (%) n = 8	X ²	p-value
Age groups (years)					0.03	0.86
20–29	30	1.5	16 (13.9)	1 (12.5)		
30–39	89	44.5	55 (47.8)	3 (37.5)		
40–49	55	27.5	33 (28.7)	3 (37.5)		
50 and above	26	13	11 (9.6)	1 (12.5)		
Sex					5.75	0.02
Female	142	71	91 (79)	4 (50)		
Male	58	29	24 (21)	4 (50)		
Marital status					0.02	0.89
Divorced	7	3.5	5 (4.3)	0 (0)		
Married	115	57.5	67 (58.3)	5 (62.5)		
Separated	6	3	4 (3.5)	0 (0)		
Single	24	12	12 (10.4)	1 (12.5)		
Widowed	48	24	27 (23.3)	2 (25)		
Education					6.87	0.01
None	15	7.5	11 (9.6)	0 (0)		
Informal	3	1.5	2 (1.7)	0 (0)		
Primary	50	25	29 (25.2)	2 (25)		
Secondary	74	37	42 (36.2)	2 (25)		
Tertiary	58	29	31 (27)	4 (50)		
Occupation					0.01	0.90
Civil servant	59	29.5	33 (28.7)	2 (25)		
Craft worker	28	14	17 (14.8)	0 (0)		
Farmers	17	8.5	8 (7.0)	1 (12.5)		
Housewife	30	15	13 (15.3)	3 (37.5)		
Student/Applicant	17	8.5	8 (7.0)	1 (12.5)		
Traders	49	24.5	36 (42.4)	1 (12.5)		
NYHA dyspnea classification					11.5	0.07
I	30	15.2	17 (15.0)	3 (37.5)		
II	16	8.1	11 (9.8)	0 (0)		
III	37	18.7	16 (14.3)	3 (37.5)		
IV	7	3.5	0 (0)	1 (12.5)		

NYHA: New York Heart Association.

concentration of TNF α , IL6,²⁰ suggesting an increase in activity of innate immune system later in life. Some argue that this increase activity of innate immune system may contribute to a long life,²¹ however elevated markers of inflammation in the aged are associated with disability and death.²²

No risk factors were identified in subjects with HRPHT. It occurred irrespective of high CD4 cell count. This again brings

to fore the question on the role of autoimmunity; inflammatory components that results from activation of innate immune system have been linked to most chronic diseases,²³ examples abounding in cardiovascular diseases involving chronic inflammation of arterial walls mediated in part by oxidized lipids.²⁴ Majority of the subjects with HRPHT in our study had significant dyspnoea when compared with the others, with 50% of them in NYHA 3 and 4 though this did not attain statistical significance. This finding is not supported by that of Petitpretz et al,¹⁶ whose patients were in NYHA 1 and 2, and younger. Again the privilege of early presentation and diagnosis, aided with the benefit of cardiac catheterization used by them, could have accounted for their results.

No association was seen between duration of highly active anti-retroviral therapy (HAART) and HRPHT. The effect of HAART on presentation of HRPHT is controversial, with some reports suggesting that it modifies presentation, while others differ.¹⁹ Some studies have reported that anti-retroviral therapy (ART) can induce endothelial dysfunction in in-vitro studies, and in animal models, resulting in increased endothelin-1 production and endothelial proliferation and thus potentially contributing to or exacerbating underlying HRPHT.^{25–27} The consensus being that for subjects who are not already diagnosed with it, early commencement could

Table 4 – Logistic regression of HRPHT and other variables.

Term	Odds ratio	95% C.I.	Z-statistic	p-Value
Age	1.00	0.89 1.12	0.05	0.96
BMI	1.12	0.89 1.39	0.98	0.33
CD4 cell count	0.99	0.99 1.00	−0.86	0.39
Duration since HIV diagnosis	0.78	0.52 1.17	−1.19	0.24
Log ₁₀ of viral load	1.26	0.42 3.82	0.41	0.68
Months on HAART	1.31	0.86 2.00	1.26	0.21
Sex	7.65	0.95 61.89	1.91	0.06
CONSTANT			−1.52	0.13

BMI: Body mass index.

Table 5 – Correlation of mPASP with selected echocardiography parameters.

2DEcho/Doppler parameter	Study population	Mean	Pearson correlation	Correlation value	p-value
EA ratio	200	1.44	0.066	Positive	0.07
EF	200	84.90	−0.284	Negative	<0.01
FS	200	35.00	−0.208	Negative	<0.01
DCT	200	192.34	−0.128	Negative	0.09
IVSD	200	14.63	0.099	Positive	0.17
IVSS	200	12.08	0.004	Positive	0.96
IVRT	200	111.86	0.077	Positive	0.29
LVIDD	200	14.58	0.126	Positive	0.08
LVPWS	200	13.75	−0.088	Negative	0.23

Correlation is significant at the 0.01 level (2-tailed).

FS: Fractional shortening, EF: Ejection fraction, DCT: Deceleration time, IVSD: Interventricular septum in diastole, IVSS: Interventricular septum in systole, IVRT: Isovolumic relaxation time, IVSS: Intra-ventricular septum thickness in systole, LVIDD: Left ventricular internal diameter in diastole, LVPWS: Left ventricular posterior wall thickness in systole.

prevent its development, and if pulmonary hypertension develops, HAART has no effect in its progression.

This study was stimulated by the cursory observation in our practice that managing heart failure in HIV-infected patients was more difficult, especially in those with evidence of pulmonary hypertension. The findings have lent credence to this assumption, as it was noticed that there was a negative correlation between pulmonary hypertension (assessed by mean pulmonary arterial systolic pressure) and such indices of left ventricular function as ejection fraction and fractional shortening, as well as deceleration time, an index of diastolic dysfunction. This is similar to the result of Acikel et al²⁸ who looked at the effect of pulmonary hypertension on left ventricular diastolic dysfunction in chronic obstructive disease. They found that deceleration time was prolonged in subjects with pulmonary hypertension compared to other patients, a finding that was replicated in ours with a tendency to prolonged isovolumic relaxation time (IVRT), and shortened deceleration time. The difference did

not reach statistical significance. Among the subjects with HRP, 25% had evidence of LV systolic dysfunction, another 25% of diastolic dysfunction, while 12.5% had pericardial effusion. This is a further confirmation of the deleterious effect of untreated pulmonary hypertension on cardiac function, re-echoed among HIV-infected patients in a facility at Washington DC, where diastolic dysfunction tended to be more common in patients with pulmonary hypertension (60% versus 36%), though the difference did not reach statistical significance.¹⁵

6. Conclusion

This study has shown that HIV infection negatively affects cardiac function and that coexisting pulmonary hypertension independently contributes to both systolic and diastolic dysfunction in the patients. The symptoms and signs of both cardiac dysfunction and pulmonary hypertension are subtle and similar to those of more common ailments such as tuberculosis, other chest infections, and anemia in HIV-infected patients. It is therefore imperative that those who care for these patients should have a high index of suspicion, so as to make early diagnosis, and ensure appropriate and timely interventions. One way of realising this is to encourage early cardiac assessment and use of echocardiography in screening these patients whose number is beginning to rise owing to the enhanced survival attributable to HAART.

Conflicts of interest

All authors have none to declare.

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Fig. 1 – Scatter diagram correlating mean pulmonary arterial systolic pressure with ejection fraction. EF: Ejection fraction (%), mPASP: Mean arterial systolic pressure mm (mmHg).

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