ORIGINAL ARTICLE

Assessment of Right Ventricular Systolic Function Using Tissue Doppler-Derived Tricuspid Lateral Annular Systolic Velocity (S`) Among HIV Patients on Highly Active Antiretroviral Therapy (HAART) And Its Relationship with CD4 Cell Count and Viral Load

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ABSTRACT

Background: Human immunodeficiency virus-infected patients are at increased risk of cardiovascular diseases compared with the general population, and right ventricular systolic dysfunction is said to be associated with poor outcomes. We therefore assessed right ventricular systolic function using tissue Doppler-derived tricuspid lateral annular systolic velocity (S`) among HIV-infected patients on highly active antiretroviral therapy (HAART). We evaluated its relationship with viral load and cd4 cells count. **Methods:** The study was a cross-sectional conducted among HIV-infected patients receiving HAART at the Federal Medical Centre, Nguru, Yobe State, Northeastern Nigeria using tissue Doppler-derived tricuspid lateral annular systolic velocity (S`). **Results**: One hundred and seven (107) subjects were recruited into the study comprising thirty-seven (34.6%) males and seventy (65.4%) females. Ninety-six (89.71%) had preserved right ventricular systolic function (RVSF) while 11(10.28%) had reduced RVSF. The mean CD4 cells count of patients with preserved RVSF and those with reduced RVSF were 838.37±27.50 and 301.66±12.38 respectively (P = <0.001). Similarly, the mean viral load of patients with preserved and reduced RVSF were 547.90±10.75 and 10293.00±74.67 respectively (P = <0.001). Pearson Correlation analysis between CD4 cell count and S` revealed a positively significant relationship (r = 0.894, P = < 0.001); while the relationship between viral load and S` was negative but significant (r = -0.879, P = < 0.001). **Conclusion:** The prevalence of right ventricular systolic dysfunction among patients with HIV on HAART was found to be 10.28%. There was a positive and significant correlation between the parameter of RVSF (tissue doppler derived tricuspid lateral annular systolic velocity) with CD4 cell count and a negative but significant correlation with HIV viral load.

Keywords: Right ventricular systolic function, Tissue Doppler derived lateral tricuspid annular systolic velocity (S`), CD4 cells, viral load.

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Introduction

Nigeria has the second highest burden of Human Immunodeficiency Virus (HIV) infection in the world, with about 3.6 million people living with the virus.[1] The introduction of highly active antiretroviral therapy (HAART) has decreased the morbidity and mortality associated with HIV infection[2]. Therefore, HIV patients live longer; however, this survival advantage is not free from complications. HIV patients are more likely to develop cardiovascular diseases than the general population, the reasons are probably multifactorial, such as the direct myocardial effect of HIV on cardiac myocytes or dendritic cells, opportunistic infections, neoplasms, autoimmunity and dietary deficiencies[3-7]. HIV infection was reported to be an established

risk factor for pulmonary hypertension[6-8,9], while on the other hand, pulmonary hypertension directly affects right ventricular function through an increase in pulmonary vascular resistance causing right ventricular hypertrophy, chamber dilatation and myocardial fibrosis[10]. Previous studies have shown that right ventricular systolic dysfunction is associated with poor outcomes[11,12]. Bassey et al in Port Harcourt-Nigeria, reported a prevalence of right ventricular systolic dysfunction among HIV-infected patients of 11.6% [13], while other researchers reported a prevalence of 11.0%[14,15]. However, there is paucity of data on right ventricular systolic function (RVSF) among HIV-infected patients on HAART in our environment. We therefore assessed the right ventricular systolic function using tissue doppler derived tricuspid lateral annular systolic velocity (s`) among HIV-infected patients on HAART and evaluated its relationship with CD4 cell count and viral load.

Study design and study population: This was a cross-sectional study conducted among asymptomatic HIV patients receiving HAART at the Federal Medical Centre, Nguru, Yobe State, Northeastern Nigeria. Patients with a positive sputum Xpert MTB/RIF assay, acid-fast bacilli or a chest X-ray suggestive of pulmonary tuberculosis (PTB) were excluded. Also excluded from the study were patients with chronic obstructive pulmonary disease, asthmatic patients, patients with a history of heart disease predating the diagnosis of HIV infection, cigarette smoking, those with known connective tissue disease or sickle cell anaemia and pregnant women. Ethical approval was obtained from the Ethics and Research Committee of the Federal Medical Centre Nguru and all subjects signed an informed consent form after being clearly explained. Sample size was calculated using the formula

$$N=\frac{Z2\ P(P-1)2}{D2}$$

Where N = Sample size, Z= Level of confidence at 95% (1.96), P = Prevalence and D = Margin of error at 5% (0.05). Using the prevalence of right ventricular systolic dysfunction among HIV patients as 11.6%, the calculated sample size was ninety-six (96). However, to enhance the strength of our study we increased our sample size to one hundred and seven (107).

Information on demographic and clinical characteristics of the patients were obtained from their respective case notes. General physical examination including anthropometric measurements were carried out for all subjects, and their body mass indices (BMI) were calculated. All patients had full cardiovascular and respiratory system examinations, fasting blood glucose, fasting lipid profile, serum electrolytes, urea, creatinine, urinalysis and packed cell volume (PCV) done. CD4 cell count and viral load estimations were done using Cyflow laser product Patec GmbH Am plus Platz 13 D028282010 and Cobas Ampliprep Cobas tagman (48 samples per batch) model 395808 Ampliprep/4312 machines, respectively. A comprehensive echocardiographic examination was carried out on all participants by the first author, using a Hitachi Prosound Aloka α6 Japan echocardiography machine with a transducer frequency range of 1-15Hz following the American Society of Echocardiography guidelines on the Assessment of the Right Heart in Adults. Right ventricular systolic dysfunction (reduced RVSF) was defined as tissue Doppler-derived tricuspid lateral annular systolic velocity (S`) less than 10cm/sec[16].

Statistical analysis was done using SPSS version 27.0 (IBM SPSS Statistics). Data are presented as mean ± standard deviation (SD) for continuous variables. Student T-test was used to compare means between groups while Pearson correlation and linear regression analysis were done to determine the relationship between CD4 cell count and viral load with S`. A p-value of < 0.05 was considered significant.

Results:

One hundred and seven subjects were recruited into the study comprising thirty-seven (34.6%) males and seventy (65.4%) females. The mean age, body mass index (BMI) and duration of HIV treatment in years of the studied subjects were 37.32±1.02, 23.52±1.21 and 5.50±1.12, respectively. Eight subjects (7.5%) with HIV were diagnosed to be hypertensive prior to the diagnosis of HIV infection while the remaining 99(92.5%) were normotensive. The mean systolic and diastolic blood pressure of the subjects were 137.66±3.52 and 82.52±2.13 respectively, none of the subjects were diabetic. All the eight hypertensive patients had optimal blood pressure control. One patient (0.93%) had HIV/Hepatitis B virus (HBV) co-infection and none had Hepatitis C virus (HCV) co-infection. The mean packed cell volume (PCV) and estimated glomerular filtration rate (eGFR) of the studied patients were 31.02±2.12 and 77.36±3.32

respectively. The mean CD4 cells count and viral load of the studied patients were 612.65 ± 34.62 cells/µL and 315.44±27.11copies/mL respectively. Table 1 showed the baseline characteristic of studied patients. Out of the 107 studied patients, ninety-six (89.71%) had preserved right ventricular systolic function (RVSF) while 11(10.28%) had reduced RVSF, all the eight hypertensive patients had preserved RVSF.

Table 1 Baseline characteristics of studied patients

Parameter	Mean value
Age in years	37.32±1.02
SBP in mmHg	137.66±3.52
DBP in mmHg	82.52±2.13
BMI in Kg/m²	23.52±1.21
Duration of Treatment in years	5.50±1.12
CD4 cells count in cells/µL	612.65 ± 34.62
Viral load in copies/mL	315.44±27.11
PCV in%	31.02±2.12
eGFR in ml/min	77.36±3.32

SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, BMI = Body Mass Index, PCV = Packed Cells Volume, eGFR = Estimated Glomerular Filtration Rate

The mean tissue Doppler-derived tricuspid lateral annular systolic velocity of patients with preserved RVSF and reduced RVSF were 11.15±1.19 and 5.80±1.23 respectively (p= <0.001). Pearson Correlation analysis between CD4 cell count and S` revealed a positive and significant relationship (r = 0.894, p = < 0.001). On the other hand, that between viral load and S` was negative and significant (r = -0.879, p = < 0.001). Linear regression analysis between CD4 cell count and S` was significant and positive (Beta = 0.894, p = < 0.001), while that between viral load and S` was negative but significant (Beta = -0.879, p = < 0.001).

There was no significant difference in the mean age and systolic blood pressure of the patients with preserved RVSF and those with reduced RVSF. However, there were significant differences in mean BMI, DBP and duration of HIV treatment between those with preserved RVSF and those with reduced RVSF. Table 2 shows the baseline characteristics of the patients with preserved RVSF and those with reduced RVSF.

Table 2: Baseline characteristics of patients with preserved and reduced right ventricular systolic function

Parameter	Preserved RVSF	Reduced RVSF	P-value
Age in years	36.74±9.62	38.11±9.43	0.465
Duration of HIV treatment in years	5.97±2.00	4.71±2.21	0.003*
SBP in mmHg	126.45±11.74	153.11±14.78	0.160
DBP in mmHg	81.29±7.57	84.22±7.22	0.046*
BMI in Kg/m²	24.80±6.68	21.77±4.90	0.012*

RVSF = Right Ventricular Systolic Function, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, BMI = Body Mass Index, * = Significant at P = < 0.05

The study also showed a statistically significant difference in mean CD4 cell count, viral load, packed cell volume, eGFR, serum creatinine and serum urea between the group with reduced RVSF (S` < 10cm/sec) and that with preserved RVSF (S` ≥ 10cm/sec). The mean CD4 cell count of patients with preserved RVSF and those with reduced RVSF were 838.37±27.50 and 301.66±12.38 respectively p = <0.001. Similarly, the mean viral load of patients with

preserved and reduced RVSF were 547.90±10.75 and 10293.00±74.67 respectively p = <0.001.

Table 3 showed the distribution of laboratory results of patients with preserved RVSF and those with reduced RVSF.

Table 3: Distribution of laboratory parameters of patients with preserved and reduced right ventricular systolic function

Parameters	Preserved RVSF	Reduced RVSF	P-value
CD4 cell count in cells/µL	838.37±27.50	301.66±12.38	< 0.001*
Viral load in copies/mL	547.90±10.75	10293.00±74.67	< 0.001*
Packed cell volume in %	33.95±3.60	27.00±5.77	< 0.001*
Serum Creatinine in µmol/L	146.93±36.37	102.96±28.84	< 0.001*
Serum Urea in mmol/L	4.97±2.05	8.39±2,79	< 0.001*
eGFR in ml/min	91.95±32.55	58.02±19.41	< 0.001*

RVSF = Right Ventricular Systolic Function, eGFR= Estimated Glomerular Filtration Rate, * = Significant at P < 0.05

Discussions

Cardiac involvement among HIV-infected patients is relatively common and is associated with increased morbidity and mortality. HIV-associated cardiovascular manifestations may be detected even in the early stage of the disease and are often asymptomatic. In this study, we found that the mean age of the patients was 37.3±1.0 years indicating that the productive age group of people are the most affected patients and female constitutes the higher proportion of patients. This finding is similar to the report by Amobi et al in their study on estimation of HIV prevalence and burden in Nigeria: a Bayesian predictive modelling study[17]. The study also showed that the mean systolic and diastolic blood pressure of the patients were within normal limit. This could perhaps be due to higher proportion of the patients been normotensive, and the comprehensive patients care services been provided at the antiretroviral (ART) clinic making it possible that even the eight hypertensive patients were having optimal blood pressure control

In this study we found a prevalence of right ventricular systolic dysfunction (reduced RVSF) among patients with HIV on treatment as 10.28%, which is lower compared to the study by Bassey et al where they reported a prevalence of 11.6% among treatment naïve patients[13]. The lower prevalence of reduced RVSF in our study could be due to the fact that our subjects were on HAART that might have restored their immunity and reduced opportunistic infections and improved the overall clinical condition and preserved the RVSF as previously reported[2,4 & 5]. The prevalence of 10.28% in our study is also lower compared to the prevalence reported by Christopher et àl[14] and Simon et àl[15] where they both reported a prevalence of 11.0% using right ventricular fractional area change. Right ventricular endocardial trabeculation may make endocardial tracing difficult which may erroneously give a false result. While on the other hand, tissue Doppler-derived lateral tricuspid annular systolic velocity that does not require endocardial tracing is more objective in assessing RVSF that perhaps explained the lower prevalence of reduced right ventricular systolic function in our study. Patients with preserved RVSF were found to have a significantly higher CD4 cells count compared to those with reduced RVSF, while on the other hand the viral load of patients with preserved RVSF was significantly lower compared to those with reduced RVSF. Furthermore, our study revealed a positive and significant correlation between CD4 cell count and a parameter of right ventricular systolic function (S`) so also on regression analysis the relationship was positive and significant. While on the other hand, the relationship between HIV viral load and S` was negative and significant on both Pearson correlation and regression analysis. This finding is similar to study by Adebola et al where they reported a positive and significant corelation between CD4 cell

count and left ventricular systolic function, though their study was on left ventricular function[18]. Reddy et al also reported a similar finding of reduced left ventricular systolic functions among HIV patients with low CD4 cell count[19]. These findings implied that overwhelming viraemia, compromised CD4 cells count and opportunistic infections causing myocarditis or dilated cardiomyopathy leading to reduced right ventricular systolic function as earlier described[3-7] Similarly, the findings also suggest that HIV infected patients with high CD4 cell count and suppressed viral load or lower viral load are likely to have preserved right ventricular systolic function while those with low CD4 cell count and high viral load are likely to have reduced RVSF. Bassey et al also reported a similar finding though using tricuspid annular plane systolic excursion to assess the right ventricular systolic function. However, their study did not report any relationship with CD4 cell count[13].

In this study, we found that there was no significant difference in the mean age of patients with preserved RVSF and those with reduced RVSF. While on the other hand, there was a significant difference in the duration of HIV treatment between the patients with preserved RVSF and those with reduced RVSF this could perhaps be due to the effect of treatment suggesting that the longer the duration of treatment, the more likely that the patient's immunity will be restored and opportunistic infections are reduced with overall clinical improvement and RVSF preserved as previously reported by other researchers[2,4,5].

Similarly, the BMI of patients with preserved RVSF is significantly higher compared to those with reduced RVSF this implies that a higher BMI in a HIV patient on treatment is associated with higher CD4 cell count and improved immune status as previously reported by Zhu et al [20]. Even though the diastolic blood pressure of the studied subjects were within normal limits, subject with reduced RVSF had significantly higher diastolic blood pressure compared to those with preserved RVSF, this perhaps might be due to hypertension (secondary to HIV associated nephropathy)[21]. While the lack of significant difference in systolic blood pressure between patients with preserved RVSF and those with reduced RVSF could be due to age similarities among the studied subjects.

Anaemia is one of the most common haematological complications associated with HIV, with increasing rate as the disease progresses[22]. In this study we found a significant difference in mean packed cell volume (PCV) of patients with reduced RVSF compared to those with preserved RVSF. Anaemia has also been reported as an independent risk factor for decreased quality of life, accelerated disease progression, and increased mortality[23,24]. HIV infection causes anaemia via direct effects of the virus itself, which may inhibit haematopoiesis through infection of progenitor cells or upregulation of cytokines[25]. Our study also revealed that patients with reduced RVSF also had reduced eGFR compared to those with preserved RVSF, this further explains the relationship between HIV infection and kidney disease as previously described[26]. The CD4 cell count of patients with preserved RVSF was found to be significantly higher compared to those with reduced RVSF, while on the other hand the viral load of patients with preserved RVSF was significantly lower compared to those with reduced RVSF. This could be due to overwhelming viraemia, compromised CD4 cell count and opportunistic infections causing myocarditis or dilated cardiomyopathy leading to reduced right ventricular systolic function as earlier described.[3-7]

Therefore, this finding of right ventricular systolic dysfunction (reduced RVSF) among HIV-infected patients could perhaps be due to overwhelming viraemia, compromised CD4 cell count and opportunistic infections causing myocarditis or dilated cardiomyopathy leading to reduced right ventricular systolic function as earlier described.[3-7] While treatment with HAART is associated with HIV viral suppression, improvement in immunological status and subsequent decrease in opportunistic infections and myocarditis, it is also seen to cause overall improvement in clinical condition[2,4,5&26]. These findings implied that HIV-infected patients when adequately treated with HAART, achieved a sustained virologic suppression and recovered immune response, right ventricular systolic function can be preserved.

In **c**onclusion therefore, our study revealed a prevalence of right ventricular systolic dysfunction (reduced RVSF) among HIV infected patients on treatment as 10.28%, and that there was a positive and significant relationship between right ventricular systolic function (tissue Doppler-derived

tricuspid lateral annular systolic velocity) with CD4 cell count and negative but significant relationship with HIV viral load.

Key words: Right ventricular systolic function, Tissue Doppler Derived Tricuspid Lateral Annular Systolic Velocity, CD4 cell, Viral Load.

Study limitations: The study was cross-sectional and thus no follow-up of the patients to determine if immune restoration and virologic suppression following adequate treatment can reverse the reduced RVSF to preserved RVSF. Secondly, the study has no control subjects to compare the right ventricular systolic function between the cases and controls, even though our exclusion criteria were robust to eliminate compounding factors. Thirdly our subjects were only one hundred and seven therefore, there is a need to have a larger multi-centred population study with follow-up to determine the relationship between RVSF, viral load and CD4 cell count.

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