RESEARCH PAPER

Echocardiographic abnormalities and disease severity (based on CD4 count) in treatment-naive HIV positive patients

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Abstract

Purpose: Human immunodeficiency virus (HIV) infection may be associated with cardiac abnormalities. These abnormalities appear to be more frequent with disease progression. This study sought to examine the relationship between HIV disease severity in treatment-naive patients and cardiac abnormalities identified by echocardiography.

Material and methods: 100 HIV-positive, treatment-naive patients, comprising 53 patients with CD4 count < 200/µl (AIDS group) and 47 patients with CD4 count ≥ 200/µl (non-AIDS group) without any traditional risk factors for cardiac disease were recruited for the study. Both groups had clinical and echocardiographic evaluation for cardiac abnormalities.

Results: Of the 53 patients in the AIDS group, 11.5% had dilated cardiomyopathy (DCM), compared with none in the non-AIDS group (p = 0.018). Systolic dysfunction was higher in the AIDS group when compared with the non-AIDS group (42.3% and 17.0%, respectively; p = 0.006). Also, those in the AIDS had a significantly higher left ventricular end diastolic diameter index when compared with the non-AIDS group (2.87 ± 0.37 and 2.67 ± 0.29, respectively; p = 0.004). Furthermore, moderate to severe pericardial effusion was more frequent in the AIDS group, when compared with non-AIDS group (15.38% and 2.12%, respectively; p = 0.045). Diastolic dysfunction was also more frequent in AIDS group, although this did not achieve statistical significance (34.64% and 29.78%, respectively; p = 0.61).

Conclusion: Cardiac abnormalities are more frequent with disease progression in HIV infected patients. Patients with more advanced disease (CD4 < 200/µl) had significantly more frequent systolic dysfunction, DCM, larger left ventricular dimension, and moderate to severe pericardial effusion than those with CD4 ≥ 200/µl.

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Introduction

HIV/AIDS is a multi-systemic disease, affecting virtually every organ and system of the body, resulting in progressive dysfunction of affected systems [1, 2]. The heart is not immune to this progressive dysfunction [3-5].

Human immunodeficiency virus (HIV) possesses an intrinsic cardiopathogenic action that may be detected even in the early stages of HIV disease [2-5]. Cardiac involvement in HIV-seropositive patients changes the natural history of the disease and is associated with increased morbidity and mortality [6].

Although it is now clear that cardiac abnormalities in HIV-seropositive patients are relatively common, they are still under appreciated, largely because they are often clinically quiescent and frequently attributed to dysfunction in other systems [7-9]. The fact that post-mortem studies found significantly higher incidence of heart diseases than the incidence of abnormalities diagnosed clinically ante-mortem is instructive [10-12].

A major issue is that not only does cardiac involvement occur early in HIV infection, but it tend to worsen as the disease progresses [7, 13-15]. The challenge is that even with the arrival of highly active antiretroviral therapy (HAART), the burden of cardiac abnormalities is likely to remain high considering the fact that late presentation remains a major concern globally, as well as number of patients with advanced HIV disease [16-18]. The aim of this study is to evaluate the association between severity of disease (using CD4 count) in treatment-naive patients and echocardiographic abnormalities.

Material and methods

Fifty-three patients with CD4 < 200/μl (AIDS group), and forty seven with CD4 ≥ 200/μl (non-AIDS group), all HAART naive, were recruited through a HIV clinic for the study. All patients had no known traditional risk factors for cardiac disease. All participants were fully briefed about the study and had a structured questionnaire administered. Both groups had clinical and echocardiographic evaluation for cardiac abnormalities as well as CD4 count.

The research was carried out in accordance with the Declaration of Helsinki. The study protocol was explained to all participants, and an informed consent was obtained from each patient. Approval for the study was obtained from the local Ethics Committee in the institution.

Results were analyzed using Epi info 2003 statistical package.

Transthoracic echocardiography was performed using Siemens Sonoline S1-450 in the cardiovascular laboratory, with a 3.5-MHZ transducer probe. Two-dimensional (2D), M-mode, pulse-wave, continuous-wave, and color Doppler echocardiography assessment was completed with the subject in the left lateral decubitus position. Left atrial diameter (LA), aortic size (AO), right ventricular outflow tract (RVOT), left ventricular end-systolic (LVEDs), and end-diastolic (LVEDd) diameters, interventricular septum (IVS), left ventricular posterior wall (LVPW), estimated right ventricle (ERV), and end-point septal separation (EPSS) measurements were obtained from 2D directed M-mode recordings from the parasternal long axis [19]. Measurements were obtained (in cm) according to the American Society of Echocardiography guidelines (leading-edge methodology) [20]. The mean of three measurements was recorded.

The following definitions were used:

- dilated left ventricle refers to LVEDd > 5.2 cm [19],
- left ventricular systolic dysfunction was determined by left ventricular fractional shortening (LVFS) < 28% [9, 21, 22],
- left ventricular fractional shortening (LVFS) (%) = $\frac{(\text{LVEDd} - \text{LVEDs}) \times 100}{\text{LVEDd}}$
- the severity of LV dysfunction was graded based on the recommendation by the ESC: mild dysfunction, fractional shortening = 22-27%; moderate = 17-21%; severe < 16% [22],
- dilated cardiomyopathy was diagnosed using three criteria: left ventricular end-diastolic diameter (LVEDd) > 5.5 cm [21, 23, 24], global hypokinesia, and fractional shortening (LVFS) < 28% [21, 25],
- isolated right heart dilatation: right ventricle and atrium larger than left ventricle and atrium, respectively, on standard two dimensional echocardiography in apical view; right ventricular end-diastolic dimension > 3.0 cm with normal left ventricular size and function [24, 26],
- doppler studies included pulmonary velocity (PV), aortic velocity (AV), transmitral flow, and deceleration time (DT) measurements. Isovolumetric relaxation time (IVRT) was obtained from pulse-wave Doppler studies [19].

Left ventricular diastolic dysfunction was diagnosed in the presence of any of the following criteria [27]:

- impaired relaxation with an E/A ratio < 1, IVRT > 100 ms, and DT > 220 ms,
- pseudonormalization resembling the normal transmitral configuration with regard to the mitral inflow, but with normal or low DT,
- restrictive pattern with E/A ratio > 2, IVRT < 70 ms, and DT < 160 ms.

Echocardiographic abnormalities, e.g., pericardial effusion, thickening, separation, valvular lesions such as stenosis, and regurgitations, and regional wall-motion abnormalities were also looked for.

Pericardial effusion refers to an echo-free space behind the left ventricle with or without an anterior echo-free space. The size of the pericardial effusion was defined as follows: small when the maximum pericardial space at end-diastole was < 1.0 cm; moderate when the space was ≥ 1.0 cm, but < 2.0 cm; and massive/severe when the pericardial space was ≥ 2.0 cm between the pericardial layers [28].

Results

The study comprised 53 patients with CD4 count < 200/µl (AIDS group), and 47 patients with CD4 count > 200/µl (non-AIDS group). There were 26 females and 21 males in the AIDS group, while the non-AIDS group consisted of 31 females and 22 males ($\chi^2 = 0.57$; $p = 0.48$). The demography and clinical features of study population is shown in Table 1.

The echocardiographic dimensions between the AIDS group and non-AIDS group are summarized in Table 2. One of the patients in the AIDS group did not have cardiac dimension measurements because large pericardial effusion precluded accurate measurements.

Comparison of left ventricular functions such as systolic and diastolic functions between the two groups is summarized in Table 3. Those in the AIDS group had significantly

Table 1. Demographic and clinical features of study population. Values are mean ± SD

Features	CD4 ≥ 200/µl (*n* = 47)	CD4 < 200/µl (*n* = 53)	*t*	*p*
Age (years)	32.15 ± 7.68	34.15 ± 7.62	1.697	0.196
BMI	23.07 ± 4.98	19.91 ± 3.92	14.889	0.000*
BSA (m^2)	1.73 ± 0.19	1.60 ± 0.17	3.522	0.0007*
Pulse rate (beats/minutes)	83.45 ± 9.32	90.29 ± 15.04	7.217	0.008*
DBP (mmHg)	72.09 ± 6.23	69.23 ± 8.13	3.783	0.055
SBP (mmHg)	114.5 ± 12.26	108.9 ± 10.26	5.955	0.016

BMI – body mass index, BSA – body surface area, DBP – diastolic blood pressure, SBP – systolic blood pressure, SD – standard deviation
**p < 0.05 is statistically significant*

Table 2. Echocardiographic dimensions in the two groups. Values are mean ± SD

Parameters	CD4 ≥ 200/µl (*n* = 47)	CD4 < 200/µl (*n* = 52)	*t*	*p*
LA (cm)	2.98 ± 0.46	2.91 ± 0.55	0.433	0.512
AO (cm)	2.73 ± 0.41	2.70 ± 0.49	0.102	0.751
ERV (cm)	2.07 ± 0.32	2.15 ± 0.52	0.971	0.327
IVS (cm)	1.00 ± 0.15	0.94 ± 0.21	3.549	0.063
LVPW (cm)	0.83 ± 0.14	0.84 ± 0.17	0.097	0.756
LVEDd (cm)	4.58 ± 0.49	4.57 ± 0.65	0.001	0.970
LVEDs (cm)	3.16 ± 0.35	3.29 ± 0.66	1.397	0.240
LVEDd/BSA (cm/m^2)	2.67 ± 0.29	2.87 ± 0.37	2.989	0.004
LVMI	142.86 ± 38.55	139.65 ± 54.54	0.335	0.739

LA – left atrial diameter, AO – aortic root diameter, ERV – estimated right ventricular diameter, IVS – interventricular septum, LVPW – posterior wall thickness, LVEDd – left ventricular end-diastolic diameter, LVEDs – left ventricular end-systolic diameter, BSA – body surface area, LVMI – left ventricular mass index
**p < 0.05 is statistically significant*

Table 3. Systolic and diastolic parameters in cases and controls. Values are mean ± SD

Parameters	CD4 ≥ 200/µl (*n* = 47)	CD4 < 200/µl (*n* = 52)	*t*	*p*
SV (cm^3)	66.51 ± 25.47	61.56 ± 24.37	0.975	0.326
LVEF (%)	66.54 ± 6.08	62.55 ± 10.10	5.516	0.021*
LVFS (%)	30.87 ± 4.64	28.45 ± 6.61	4.808	0.031*
DT (s)	181.50 ± 28.44	193.5 ± 31.18	3.955	0.050
IVRT (s)	84.70 ± 17.67	91.30 ± 20.87	2.909	0.091
EPPS (cm)	0.410 ± 0.208	0.481 ± 0.377	1.312	0.255

SV – stroke volume, LVEF – left ventricular ejection fraction, LVFS – left ventricular fractional shortening, DT –deceleration time, IVRT – isovolumic relaxation time, E/A – ratio of early (E) to late (A) diastolic filling velocities in the mitral inflow
**p < 0.05 is statistically significant*

Table 4. The impact of disease severity on echocardiographic abnormalities in HIV patients with CD4 < 200/µl and > 200/µl. Values are number (%)

Echocardiographic abnormalities	CD4 < 200/µl (*n* = 52)	CD4 ≥ 200/µl (*n* = 47)	χ^2	*p*
Pericardial effusion*	27 (50.94)	21 (44.68)	0.39	0.532
Moderate to severe pericardial effusion	8 (15.01)	1 (2.12)	2.79	0.045
Systolic dysfunction	22 (42.30)	8 (17.02)	7.47	0.006
Diastolic dysfunction	18 (34.62)	14 (29.78)	0.26	0.608
Dilated cardiomyopathy	6 (11.32)	0 (0.00	2.95	0.018
Isolated right-sided dilatation	1 (1.92)	0 (0.00)	0.12	1.000
Total valvular regurgitations	16 (30.77)	8 (17.02)	2.54	0.111
Mitral regurgitation	11 (21.15)	5 (10.64)	2.01	0.156
Tricuspid valve regurgitation	8 (15.09)	4 (8.51)	0.54	0.460
Aortic regurgitation	3 (5.77)	1 (2.12)	0.17	0.619
Pulmonary regurgitation	6 (11.53)	1 (2.12)	2.05	0.115

**N = 53 cases in patients with CD4 < 200/µl for pericardial effusion*
p < 0.05 is significant

reduced systolic parameters (LVFS, LVEF) when compared with the non-AIDS group.

The frequency distribution of echocardiographic abnormalities in relation to the disease severity (CD4 count) is summarized in Table 4. Echocardiographic abnormalities were more frequent in the AIDS group compared with the non-AIDS group. Furthermore, systolic dysfunction, moderate to severe pericardial effusion, and dilated cardiomyopathy were significantly more frequent in the AIDS group as well.

Discussion

This study reveals that cardiac abnormalities are more frequent in patients with AIDS. Furthermore, the severity of cardiac abnormalities is worse in this group of patients, suggesting that disease progression results in worsening cardiac pathology. This trend has been reported by other researchers [3, 9, 11].

In this study, pericardial effusion, a common cardiac abnormality in HIV patients, was more frequent in patients with AIDS; with moderate to severe effusion significantly commoner in this group. Silva-Cardos *et al.* [29] in similar study involving 181 HIV-positive patients reported moderate to severe pericardial effusion in 13% of the total subjects studied. These effusions were also more frequent in advanced stage of the disease.

Pericardial disease is the most frequent cardiovascular manifestation of HIV infection [28, 30, 31], and it is often associated with shortened survival. Heidenreich *et al.* [32] in a 5-year follow-up study of patients with HIV reported that more subjects with AIDS developed pericardial effusion compared with the non-AIDS group. Furthermore, the survival of AIDS patients with effusion was significantly shorter (36% at 6 months) when compared with AIDS patients without effusion (93% at 6 months).

The findings in our study may be due to the interplay of factors that become more expressive as immunodeficiency state of patients worsens. Various causes of pericardial effusion, ranging from tuberculosis (the commonest cause) to opportunistic infections such as cytomegalovirus, mycobacterium, *Cryptococcus*, bacterial infections, malignancies such as Kaposi's sarcoma, non-Hodgkin lymphoma, and enhanced cytokine expression are all commoner in severely immunodeficient patients [29, 32], increasing the risk of developing clinically significant pericardial effusion.

Although, no definitive cause of pericardial effusion was determined in our study, one of the AIDS patients with massive pericardial effusion actually had Kaposi sarcoma, and about half of the other patients had tuberculosis. It must also be stated that HIV, which on its own can cause pericardial effusion, becomes more pathogenic as the disease progresses [3]. Aggressive management of HIV to prevent/reduce opportunistic infections and slow down the progression of the disease may reduce the prevalence of pericardial effusion in these patients.

Left ventricular (LV) dysfunction is often found in the early stage of Human immunodeficiency virus (HIV) infection and deteriorates with disease progression [13]. Our study also reveal that the severity of immunodeficiency in HIV patients is associated with increased frequency and worsening of left ventricular dysfunction. Silva-Cardoso *et al.* [33] reported similar finding in a study that recruited 98 HIV-positive patients in Portugal, where systolic dysfunction was noted to be worse with disease progression. Similar trend had been noted in other studies [9, 11, 15].

The etiology of systolic dysfunction in HIV patients is also multifactorial [3, 4, 11, 13, 33]. There is an established correlation between severity of immunodeficiency and worsening subclinical myocardial inflammation caused by HIV and opportunistic infections [2, 3, 5, 6], autoimmunity [1, 3, 5, 31, 34], micronutrient deficiency like selenium and other trace elements (due to malabsorption, diarrhea, and wasting syndrome) [4, 10, 23, 25, 35], and cytokine activation [1, 3, 10, 25, 33, 34]. Myocardial macrophage and endothelial cell infiltration, activation of cytokine, cardiomyocyte expression of HIV-associated protein, gp-120, and transactivator of transcription (Tat) protein signaling pathways have been implicated in mitochondrial dysfunction and cardiomyocyte apoptosis, resulting in worsening left ventricular systolic dysfunction [10, 33-35].

Although, the possible etiologies of systolic dysfunction were not determined in our study, most of the patients in the AIDS group had opportunistic infections, diarrhea with obvious evidence of wasting syndrome, their BMI and BSA significantly smaller than the non-AIDS group. One patient also had Kaposi sarcoma, as mentioned earlier. The resultant nutritional deficiencies and probable myocardial inflammation with cytokine activation, mitochondrial injury, apoptosis, and autoimmunity are possible major players in the development and worsening systolic dysfunction in these patients.

Systolic dysfunction is an important cause of morbidity and mortality in AIDS patients that changes the natural course of the disease significantly, even if they are asymptomatic as most patients are initially [36, 37]. With this in mind, it is imperative to have early recognition of dysfunction and institution of management, as this may impact on the overall outcome of these patients. It is a recognized fact that patients will usually respond to early therapy for left ventricular dysfunction, resulting in improved quality and duration of life [35, 38]. It may not be out of place therefore, to have mandatory cardiovascular evaluation, especially for patients whose CD4 is < 200/μl.

Diastolic dysfunction was also found to be more frequent in patients with CD4 < 200/μl in our study, although not statistically significant. Indices of diastolic dysfunction, IVRT, and DT were prolonged in the AIDS group, though not statistically significant. Perhaps a larger sample size might have been more revealing. Similar findings were reported by Cardoso *et al.* [33] and Coudray *et al.* [39]. The more commonly mentioned parameter in literature that changes significantly in HIV patients is the IVRT and the report generally reveal initial prolongation (correlating with impaired relaxation), and subsequent reduction, signifying decreased compliance and increased stiffness as the disease progresses [13].

Possible causes of diastolic dysfunction include chronic inflammation and increased cytokine expression, which worsens with disease severity. Also, disease severity is associated with autoimmunity and subclinical atherosclerosis, which are documented causes of diastolic dysfunction [40].

DCM is a well-documented cardiac abnormality in HIV/AIDS, frequently associated with advanced immunodeficiency, and poorer prognosis [9, 23-25, 28, 38]. HIV-associated cardiomyopathy (HIVAC) is a stage IV, HIV-defining illness, and remains a significant cause of morbidity and mortality among HIV-infected individuals despite ART [34]. In our study, all patients with DCM had more advanced immunosuppression with a mean CD4 count of less than 100/μl. The result corroborates several reports that dilated cardiomyopathy in HIV is associated with advanced immunosuppression and lower CD4 lymphocyte counts < 100/μl [5, 9, 24, 39]. Only two of the lot had overt symptoms of heart failure; this further underscores the fact that most cardiac abnormalities in HIV/AIDS patients are clinically quiescent, and the need for early and periodic cardiovascular evaluation of these patients cannot be overemphasized [28, 38].

One of the patients with advanced immunosuppression had isolated right ventricular dilatation and dysfunction, which has been reported as an associate of disease progression and poorer prognosis in other publications [15, 24, 26].

Although no definitive etiologies were determined for HIVAC in our study, possible postulations may apply. Generally, the degree of immunodeficiency in HIV patients may enhance the pathogenic action of both HIV and other cardiotropic viruses, or may favor the selection of viral variants of increased pathogenicity, influencing the development of cardiac abnormalities [1-5, 10, 12]. In the setting of worsening immunosuppression, the adverse effects of possible increased expression of viral proteins and transcriptional activation of various cellular genes, with resultant interference with beta adrenergic stimulation, cardiac apoptosis, and mitochondrial dysfunction may be further pathogenetic factors in inducing cardiomyopathy in these patients [3, 33, 34]. Also, an increased expression of cytokines, worsening endothelial dysfunction, and nutritional deficiencies are documented major causes of HIVAC in advanced immunosuppression [34, 35].

Cardiovascular disease (CVD) is one of the leading cause of morbidity and mortality in HIV patients [34, 35, 41]. This solemn reality is quite disturbing, increasing the already stretched global cardiovascular burden. This is even worse in our region with scare resources for management.

Observational data suggest that HAART, by preserving immune function and preventing profound immunosuppression, reduces the incidence of HIV related heart disease [39-42]. The rate of progression from left ventricular dysfunction to heart failure can be considerably slowed by HAART therapy [15]. Although there is no conclusive evidence that HAART reverses cardiomyopathy, it appears, however, that by preventing profound immunosuppression and the development of AIDS, heart muscle remain healthier [41-43]. Therefore, a major focus on prevention and treatment strategies for HIV-related heart disease in developing countries should include, among others, an aggressive campaign to get universal access to HAART. It will be worth the while to encourage physicians to perform HIV testing more frequently in order to detect HIV infection early, and commence management without delay where necessary.

Our study did not look directly at the possible impact of other comorbidities like HIV-associated nephropathy, anemia, or dyslipidemia, which may impact the cardiac abnormalities. The prognostic implication of the cardiac pathologies was also not assessed. It will be interesting to assess the response of patients to HAART prospectively.

Conclusions

Cardiac abnormalities are more frequent and more severe with disease progression in HIV-infected patients, suggesting that disease progression results in worsening cardiac pathology. With this in mind, early recognition of dysfunction and institution of management is imperative, as this may impact the overall outcome of HIV-positive patients.

Conflict of interest

The author's declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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