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Cardiomyopathy and Heart Failure

Evaluation of Subtle Left Ventricular Systolic Dysfunction by Longitudinal Systolic Strain in Patients with Human Immunodeficiency Virus

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Background: Although left ventricular systolic dysfunction (LVSD) is a major cause of morbidity in human immunodeficiency virus (HIV)-infected patients, there is limited data on cardiac functions of these patients. Compared to the conventional echocardiography, the global longitudinal strain (GLS) can detect subclinical myocardial dysfunction at an earlier stage.

Objectives: In our study, we aimed to evaluate left ventricular systolic functions using the GLS in HIV-infected patients and to investigate the effect of cluster of differentiation 4 T-cell values on LVSD.

Methods: This prospective, case-control study included a total of 65 HIV-infected patients and 48 healthy volunteers. Conventional and strain echocardiography were performed on all participants. In HIV-infected patients, CD4 T-cell counts and HIV-ribonucleic acid (HIV-RNA) values were measured.

Results: The median CD4 T-cell count was 529.65 cells/mm^3 in the HIV-infected patients and median duration of living with HIV was 16.25 (range: 2 to 120) months. Baseline characteristics and left ventricular ejection fraction values were similar in both groups. However, there was a significant difference in the low-density lipoprotein cholesterol, triglycerides, interventricular septum, left ventricular posterior wall, and GLS between the groups ($p = 0.013$, $p = 0.005$, 0.041, $p = 0.013$, and $p = 0.003$, respectively). There was a positive correlation between GLS and CD4 levels ($r = 0.463$, $p < 0.001$).

Conclusions: Our study results suggest that reduced CD4 T-cell counts in HIV-infected patients may cause myocardial dysfunction and GLS can be useful to show subtle LVSD asymptomatic cases.

Key Words: CD4 T cell • HIV infections • Left ventricular dysfunction • Longitudinal strain

INTRODUCTION

Heart failure is a major cause of morbidity and mortality in patients infected with human immunodeficiency virus (HIV).[1] The incidence of heart failure in HIV-infected patients varies from country to country. In addition, its incidence in HIV-1 infected patients receiving antiretroviral treatment is often about four times more than in the normal population.[2]

Low baseline cluster of differentiation 4 T-cell counts and high viral load are the main indicators in the development of heart failure in HIV-infected patients.[3] HIV, which invades the myocardial tissue, is also known to cause myocardial inflammation and may lead to heart failure.[4] Previous studies have shown that CD4 T-cells also have effects on myocardial healing and remodeling,[5] and there is a relationship between low baseline CD4 T-cell counts and worsening of heart failure.[6]

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Heart failure in HIV-infected patients is usually recognized late, as it is mildly symptomatic or asymptomatic.[3] Although conventional echocardiography is widely used to assess left ventricular (LV) myocardial function,[7] the global longitudinal strain (GLS) reflects LV systolic functions more accurately and detects early LV systolic dysfunction (LVSD).[8] In addition, it has a prognostic value for patients with normal or near normal LVEF in terms of showing global cardiac functions.[9]

As heart failure is often recognized late in HIV-infected patients, early detection of LVSD is critical. In the present study, we aimed to evaluate early LVSD with GLS in HIV-infected patients and to investigate the effect of CD4 counts on GLS.

MATERIALS AND METHOD

Study population

The study was approved by the local ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki. A written informed consent was obtained from each participant. This prospective, single-center, case-control study included a total of 65 HIV-infected outpatients, and 48 age- and sex-matched healthy volunteers in the tertiary referral hospital. Participants were excluded if they had diabetes, hypertension, any renal disease, history of cardiovascular event (coronary artery disease or cerebrovascular disease), moderate or severe heart valve disease, atrial fibrillation or flutter, cancer, or thyroid dysfunction. Initially, data including medical history, clinical characteristics, physical examination findings, systolic and diastolic blood pressure measurements, and 12-lead electrocardiograms were recorded.

Echocardiographic measurements

All examinations were performed using a machine by the same sonographer who was unaware of the subjects' subgroup. Traditional and strain echocardiographic measurement analyses were performed by two cardiologists who were blinded to the patients' demographic parameters for all participants. All echocardiographic studies were performed on a Philips IE 33 system (Medical Healthcare Inc. Andover, MA, USA) and used a 5-1 1.5-3.6 MHz transducer. Post-processing analysis of software for strain imaging was done by QLAB 9 [cardiac motion quantification (CMQ); Phillips Medical Systems]. Three successive cardiac cycles of three apical views were acquired and saved as a raw data during breath holding for post-processing analysis. Single-lead ECG recordings were obtained simultaneously and all were sinus rhythm at the time of examination. All the echocardiographic measurements were taken according to the guidelines.[10]

Two-dimensional, M-mode, and color-flow Doppler echocardiography was performed according to the standard techniques. The LV ejection fraction (LVEF) was measured with the biplane Simpson method by manually tracing the digital image in the apical four-chamber view. LV end diastolic dimensions were measured using the mitral valve leaflet side in the parasternal long axis view. Interventricular septum and LV posterior wall measurements were performed using the same region. Right ventricle and atrium were measured using 2D echocardiography in the apical 4-chamber view. The tricuspid annular plane systolic excursion (TAPSE) was measured in the apical 4-chamber view using M-mode echocardiography to determine the lateral tricuspid annulus motion. The Devereux formula was used for calculating LV mass (LVM)[11] and LV mass index (LVMI) was measured by dividing the LVM into the body surface area.

The GLS was assessed using speckle tracking echocardiography. For each of the apical views [two-chamber (2CH), 3CH and 4CH], three sampling points were placed manually at the septal and lateral mitral annuli and at the apical endocardium. The software automatically displayed an epicardial tracing to include the entire myocardial width, and was later adjusted manually for optimal tracking. The tracking quality provided could then be approved or rejected by the observer. Scanned apical views were avoided as foreshortening affects the result of Speckle-tracking echocardiography. We avoided premature beats and chose the best cardiac cycles to achieve optimal tracking analysis.

Fifteen participants were included for traditional and strain echocardiography reproducibility analysis. Three weeks later, the first physician re-analyzed the echocardiographic images of the participants. Intra-observer reproducibility was determined by an echocardiographer's own analysis, while inter-observer reproducibility was determined by the analyses of two echocardiographers.

Laboratory analysis

Hemogram, biochemistry and thyroid-stimulating hormone were calculated through impedance, photometric and immunoassay method respectively. HIV was determined by enzyme-linked immunosorbent assay (ELİSA) test, and then a positive result is confirmed by Western Blot test on the blood specimen. CD4 T-cell counts were calculated using a flow cytometer (Facscan flow cytometer, Benkton Dickinson, San Jose, CA, USA). CD4 T-cell counts in the patients who experienced antiretroviral therapy (ART) were calculated as the final CD4 T-cell counts before ART was initiated. CD4 T-cell counts of the patients who were ART-naïve were calculated at the time of enrollment. In addition, HIV-ribonucleic acid (HIV-RNA) was detected using the COBAS AmpliPrep/ COBAS TaqMan HIV-1 Test (Roche Molecular Systems, Branchburg, USA). These values were based on the values at the time of enrollment. The values below 50 copies/mL were defined as HIV under control, while 50 copies/mL and above were defined as uncontrolled.

Statistical analysis

Statistical analysis was performed using SPSS 16 software (SPSS Inc., Chicago, Illinois). Data are reported as mean ± SD for continuous variables. Categorical variables are reported as percentages. The normality assumption was evaluated by the Kolmogorov-Smirnov test. Continuous variables were compared between two groups using an independent samples t-test or Mann-Whitney U test. Categorical data were compared using the chi-square or Fischer exact test. Pearson's correlation analysis was performed for the variables that were normally distributed, whereas Spearman's correlation analysis was performed for the variables that were not normally distributed. Partial correlation analysis was performed between GLS and CD4, and LVMI and glucose were controlled.

A p value of less than 0.05 was considered statistically significant. Coefficient of variation analysis was performed to intra- and inter-observer reproducibility for traditional and speckle tracking echocardiography.

RESULTS

We enrolled 113 participants who were divided into two groups according to presence of HIV infection; the HIV-infected group waslabeled HIV (+) (n = 65, mean age 33 ± 7, 92% male), the non-infected HIV group was labeled HIV (-) (n = 48, mean age 32 ± 7, 90% male).

The clinical, demographic features and the laboratory findings for the two groups are shown in Table 1.

Table 1. Demographic, clinical and laboratory parameters of subjects with or without HIV

	HIV (+) (n: 65)	HIV (-) (n: 48)	p value
Age (years)	33.35 ± 7.32	31.52 ± 7.43	0.192
Male n (%)	60 (92)	43 (90)	0.741
Family history n (%)	12 (18.5)	10 (20.8)	0.81
Smoker n (%)	37 (56.9)	30 (62.5)	0.568
BMI (kg/m^2)	24.29 ± 2.82	23.71 ± 2.20	0.219
Systolic blood pressure (mm Hg)	114.92 ± 10.17	114.27 ± 8.12	0.219
Diastolic blood pressure (mm Hg)	74.15 ± 8.64	72.71 ± 6.27	0.305
Fasting glucose (mg/dl)	91	89	0.053
Creatinine (mg/dl)	0.91 ± 0.13	0.91 ± 0.16	0.855
Total cholesterol (mg/dl)	176.31 ± 38.27	165.48 ± 24.34	0.070
LDL-C (mg/dl)	107.09 ± 31.40	94.54 ± 21.13	0.013
Triglycerides (mg/dl)	125 (87-182)	94 (68-129)	0.005
TSH (μIU/ml)	1.80 ± 0.87	1.73 ± 0.86	0.658
WBC (cells/mm^3)	6557 ± 2113	6977 ± 1533	0.224
Viral loads (< 50 copies/ml) n (%)	43 (66)	-	(N/A)
Duration of HIV (months)	16.25	-	(N/A)
ARV use n (%)	48 (74)	-	(N/A)
CD4 T cell count (cells/mm^3)	529.65	-	(N/A)

ARV, antiretroviral; BMI, body mass index; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus; LDL-C, low density lipoprotein cholesterol; TSH, thyroid-stimulating hormone; WBC, white blood cells.

There were no significant differences among the groups with respect to age, sex, smoking, body mass index (BMI), systolic and diastolic blood pressure, creatinine, fasting blood glucose, total cholesterol, and white blood cell count ($p > 0.05$ for all; Table 1). LDL-C, and triglycerides were significantly higher in HIV (+) compared with HIV (-) ($p = 0.013$, $p = 0.035$, $p = 0.005$, respectively, Table 1). The median duration of HIV infection was 16.25 months (range: 2 to 120) in the patient group. A total of 66% of HIV-infected patients also had viral load under control, while 74% received ART. The mean CD4 T-cell count was 529.65 cells/mm^3.

Echocardiographic parameters of the HIV patients and the control group are shown in Table 2. Echocardiographic parameters including LVEDd, LVESd, LVEF TAPSE, E, E/E' and LVMI were similar between the two groups (Table 2). GLSs were statistically significant in HIV (+) compared to HIV (-) patients ($p = 0.003$, Table 2).

The correlation analyses of the HIV-infected patients are shown in Table 3. CD4 T cell counts was positive correlated with GLS. Fasting glucose inversely less correlated with GLS. There was no correlation between GLS and age, BMI, smoking years, systolic and diastolic blood pressure and LVEDd. Partial correlation analysis showed that CD4 T-cell counts were moderately correlated with GLS.

The relationship between different CD4 cell levels and GLS is shown in Table 4. No significant difference was observed with different CD4 levels and GLS.

Table 2. Echocardiographic parameters of subjects with and without HIV

	HIV (+) (n: 65)	HIV (-) (n: 48)	p value
LVEDd (mm)	48.30 ± 4.14	49.44 ± 3.53	0.119
LVESd (mm)	32.55 ± 3.63	32.66 ± 2.77	0.857
IVS (mm)	10.07 ± 1.00	9.67 ± 1.04	0.041
LVPW (mm)	9.71 ± 1.03	9.27 ± 0.84	0.013
LVEF (%)	60.74 ± 1.89	61.14 ± 1.86	0.264
LAd (mm)	33.40 ± 3.02	32.16 ± 3.30	0.044
TAPSE (cm)	2.39 ± 0.27	2.42 ± 0.27	0.582
GLS (%)	18 (17-20)	20 (18-22)	0.003
LVMI (g/m^2)	89.75 ± 16.91	89.19 ± 15.71	0.856
E (cm/s)	81.84 ± 11.92	83.25 ± 10.62	0.519
E' (cm/s)	13.70 ± 3.24	14.16 ± 2.92	0.444
E/E' ratio	6.32 ± 1.88	6.07 ± 1.17	0.416

E, early diastolic mitral inflow velocity; E', early diastolic mitral annular velocity; GLS, global longitudional strain; HIV, human immunodeficiency virus; IVS, interventricular septum; LAd, left atrium diametr; LVEDd, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESd, left ventricular end systolic diameter; LVMI, left ventricular mass index; LVPW, left ventricular posterior wall; TAPSE, tricuspid annular plane systolic excursion.

Table 3. Correlation between GLS with demographic and echocardiographic parameters in patients HIV

	Bivariate correlation		Partial correlation	
	R	p value	R	p value
Age (years)	-0.043	0.735		
BMI (kg/m^2)	0.211	0.092		
Smoking years (years)	-0.201	0.108		
Systolic blood pressure (mm Hg)	0.153	0.225		
Diastolic blood pressure (mm Hg)	0.133	0.291		
Fasting glucose (mg/dl)	-0.297	0.016		
LDL-C (mg/dl)	-0.089	0.483		
Triglycerides (mg/dl)	-0.182	0.148		
LVEDd (mm)	-0.078	0.539		
LAd (mm)	0.169	0.179		
CD4 T cell count (cells/mm^3)	0.463	< 0.001	0.319	0.011
LVMI (g/m^2)	0.109	0.389		
E' velocity (cm/s)	-0.204	0.104		
E/E' ratio	-0.091	0.472		

BMI, body mass index; CD4, cluster of differentiation 4; E, early diastolic mitral inflow velocity; E', early diastolic mitral annular velocity; GLS, global longitudional strain; HIV, human immunodeficiency virus; IVS, interventricular septum; LAd, Left atrium diametr; LDL-C, low density lipoprotein; LVEDd, left ventricular end diastolic diameter; LVMI, left ventricular mass index; LVPW, left ventricular posterior wall.

Table 4. GLS relationhip between different CD4 T cell levels

	GLS	p value
CD4 < 300 (n: 11)	17.82 ± 2.32	0.230
CD4 > 300 (n: 54)	18.61 ± 1.91	
CD4 < 500 (n: 35)	18.34 ± 1.97	0.585
CD4 > 500 (n: 30)	18.63 ± 2.03	

CD4, cluster of differentiation 4; GLS, global longitudinal strain.

Intra- and inter-observer coefficients of variation were found to be < 5% in all traditional echocardiography and < 15% speckle tracking echocardiography.

DISCUSSION

The main finding of the present study is that HIV-infected patients with normal LV systolic functions without cardiac symptoms had lower GLS than healthy individuals. In addition, there was a positive correlation between CD4 and GLS in HIV-infected patients. To the best of our knowledge, there are a few studies related to this subject.

Onur et al.[12] compared Doppler strain imaging parameters of the systolic tissue among asymptomatic HIV-infected patients and healthy individuals and found that lateral and septal systolic strains were lower, despite the fact that LV systolic function in HIV-infected patients was preserved. In addition, the authors found no relationship between CD4 T-cells and systolic strain. In another study, Karavidas et al.[13] investigated anterior, septal, lateral, and posterior systolic strains in both HIV-infected and uninfected individuals with normal and similar LV systolic functions. Although HIV-infected patients had lower systolic strain, an association between CD4 T-cells and strain was not indicated. Similar to previous studies, in our study, LV systolic function parameters such as LVEF of asymptomatic HIV-infected patients were normal as assessed by standard echocardiography, and their GLS values were lower in HIV-infected patients than those in the control group. However, in the present study, unlike the aforementioned study, there was a positive correlation between CD4 T-cell count and GLS.

Furthermore, cardiovascular diseases are observed requently in HIV-infected patients in the era of highly active ART. Coronary artery disease, cerebrovascular disease, and HIV-associated cardiomyopathy are more common among these diseases.[14,15] HIV-associated cardiomyopathy often occurs as reduced LVEF or dilated LV.[2] Several mechanisms have been identified in relation to the development of heart failure in HIV-infected patients, such as direct effect of HIV, autoimmunity, chronic inflammation, coronary artery disease or side effects of ART.[3] The combination of immunodeficiency and high viral load has been described in all of these mechanisms.[2] Increased inflammatory markers have also been suggested in HIV-infected patients.[16] Autopsy reports of patients who died in the pre-ART era due to acquired immune deficiency syndrome showed histopathological myocarditis traces at a rate of more than 50%.[17] In a cardiac magnetic resonance imaging study conducted by Luetkens et al.,[18] a higher rate of myocardial fibrosis was detected in HIV-infected patients (82.1%) than in the healthy control group (27.3%). In an adult postmortem study, Liu et al.[19] reported that HIV invasion was detected in LV myocardium of HIV-infected patients.

In addition, it has been suggested that activated CD4 T-cells of HIV-infected patients may cause cardiomyopathy and associated heart disease by causing myocarditis and inflammatory responses.[4] Although interferon gamma and interleukin-12 released from T-cells are associated with the inflammatory process, these cytokines also cause a reduction of collagen deposition.[20] In addition, previous studies have demonstrated that CD4 T-cells have an anti-fibrotic effect and may be effective in wound healing under different experimental conditions.[21,23] In one study, Hofmann et al.[5] reported that CD4 deficiency in a mouse model with induced myocardial infarction was associated with increased cardiac inflammation, impaired wound healing, LV remodeling, and impaired survival. In addition, a reduction in circulating CD4 T-cells was associated with an increased rate of hospital admission due to impaired LV function and cardiac insufficiency.[6] The clinical vignette of heart failure is usually diagnosed at an advanced stage due to its temporary symptomatic or asymptomatic status in HIV-infected patients.[3]

Currently, LVEF is one of the most commonly used markers to evaluate LV systolic function, as assessed by conventional echocardiography.[7] However, this method has several limitations such as geometric assumptions, foreshortening, load dependency, inter-observer variability, and the influence of the heart rate. The GLS is a

semi-automatic and very useful tool which is not affected by geometric assumption using speckle-tracking echocardiography, and it is helpful to assess LV myocardium function owing to its multi-dimensional myocardial mechanic properties. This method has also been shown to evaluate LV systolic functions more comprehensively and reliably than conventional echocardiography methods.[8-24] In addition to being a validated tool for LV longitudinal deformation measurements, it is more physiological in visualizing global cardiac functions.[9,25] It is an important markerto detect subclinical LVSD with a high sensitivity and specificity rate.[8] Myocardial fibrosis and scar tissue may cause decreased myocardial contractility which can be overlooked by conventional echocardiography. However, a longitudinal strain can be used to overcome this challenge.[26] A low level of CD4 T-cells may lead to myocardial fibrosis and scar tissue.[5] Unlike other studies,[12,13] the present study attributes the existence of the relationship between CD4 level and GLS to a higher number of patient admissions compared to the other studies and the use of the basal CD4 level instead of the current CD4.

Despite the similarity of LVEF in both groups of the present study, lower GLS was found in HIV-infected patients. This decline was more significant in those with low CD4 T-cell counts. This can be attributed to the direct or indirect effects of HIV on the myocardium and limited antifibrotic effects of low CD4 T-cells, thereby, leading to remodeling.

Limitations

Nonetheless, there are some limitations to this study. First, imaging and biochemical variables as indicators of myocardial fibrosis were unable to be investigated. Second, CD4 T-cell counts were only measured in HIV-infected patients, and not in healthy individuals. Finally, a relatively small sample size and inadequate representation of women can be regarded as the other limitations.

CONCLUSIONS

In conclusion, based on our study results, GLS can be used in the diagnosis of subclinical LVSD which is often overlooked by conventional echocardiography in asymptomatic HIV-infected cases. In addition, patients with low CD4 T-cell counts should be cautiously examined for subclinical myocardial systolic dysfunction, although further large-scale, long-term studies are required to establish a definite conclusion.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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