Left Ventricular Dysfunction is Associated with CD4 Lymphocyte Count rather than Opportunistic Infection in Human Immunodeficiency Virus Infection

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Background and Purpose: Left ventricular (LV) dysfunction is often found in the early stage of human immunodeficiency virus (HIV) infection and deteriorates with disease progression. CD4 lymphocyte count and opportunistic infection are the major indicators for the clinical staging of HIV infection. This study investigated the association of these indicators with LV dysfunction in the clinical course of HIV infection.

Methods: HIV-positive patients without cardiac manifestations consecutively admitted from May 1998 to April 1999 were enrolled in the study. Echocardiographic LV function evaluation and measurement of CD4 lymphocyte count were performed. Parameters for LV systolic and diastolic functions were compared between patients with CD4 lymphocyte count ≥ 200/μL and those with CD4 < 200/μL. In patients with CD4 < 200/μL, LV function was further correlated with the presence or absence of opportunistic infections.

Results: Ninety eight HIV-positive patients including 52 with CD4 ≥ 200/μL and 46 with CD4 < 200/μL were studied. One half of the 46 patients with CD4 < 200/μL had active opportunistic infections. We found that LV fractional shortening, ejection fraction, and isovolumic relaxation time were all significantly lower in the patients with CD4 < 200/μL compared with those with CD4 ≥ 200/μL. Moreover, these LV systolic and diastolic dysfunctions were positively correlated with decreased CD4 lymphocyte count. In contrast, no difference was found in these parameters between patients with and without opportunistic infections. In multiple regression analysis, CD4 lymphocyte count was found to be the only factor for predicting the LV systolic and diastolic dysfunction.

Conclusions: Both LV systolic and diastolic function deteriorate as the CD4 lymphocyte count decreases in HIV infection. Opportunistic infection seems to have a limited role in the pathogenesis of LV dysfunction in advanced HIV infection.

Key words: Ventricular function, left; HIV; CD4 lymphocyte count; Opportunistic infections

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Left ventricular (LV) dysfunction has been described in patients with human immunodeficiency virus (HIV) infection.[1–7] Initially, clinical manifestations of LV dysfunction were mostly noted in patients with advanced HIV disease such as acquired immunodeficiency syndrome (AIDS). Later reports found that abnormalities including LV systolic and diastolic dysfunction could be detected even in asymptomatic seropositive carriers at the early stage of HIV infection.[8–11]

Several authors further demonstrated that the incidence of LV dysfunction increases as the disease progresses from asymptomatic HIV carrier status to AIDS.[2,3,6,8,11] However, the pathogenic process of LV dysfunction as it develops in the disease course of HIV infection remains unclear.

In the clinical course of HIV infection, CD4 lymphocyte count decreases with disease progression. When CD4 lymphocyte count falls below 200/μL, the incidence of opportunistic infections increases.[12–17] As CD4 lymphocyte count and opportunistic infection constitute the major components for clinical staging of HIV infection,[18] both have been considered to be correlated with LV dysfunction in the disease process. However, literature reviews have yielded controversial results. Currie et al,[7] Herskowitz et al,[8,19] Barbaro et al,[20] and Barbaro and Di Lorenzo[21] demonstrated that LV dysfunction was associated with lower CD4 counts, while

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Blanchard et al[22] showed no significant correlation between CD4 count and abnormal LV function. On the other hand, Cardoso et al[11] found that congestive heart failure and abnormal transmitral flow pattern were more prevalent in patients with active infections, while Levy et al[2] and Herskowitz et al[19] found no specific relationships between cardiac dysfunction and opportunistic infections.

Given that opportunistic infections usually occur in patients with low CD4 lymphocyte count, both factors contribute to the development of LV dysfunction in advanced HIV infection. The purpose of this study was to clarify the associations of CD4 lymphocyte count and opportunistic infection with LV dysfunction at different clinical stages of HIV infection.

Methods

From May 1, 1998 to April 30, 1999, HIV-seropositive patients free from cardiac symptoms who were treated at National Taiwan University Hospital or Taipei Municipal Venereal Disease Control Center were enrolled and underwent echocardiographic evaluation of LV systolic and diastolic function.

At the time of inclusion, the patients' age, gender, body height, body weight, pulse rate, systolic blood pressure, diastolic blood pressure, and mean blood pressure, and the existence of opportunistic infection, were recorded. Opportunistic infection in this study was defined as clinically evident infection with microbiological, serological, or pathological confirmation at the time of echocardiographic evaluation. These patients also underwent hematological and serological assessment, including white blood cell (WBC) count, hemoglobin, fractions of neutrophils and lymphocytes, absolute neutrophil count, CD4 lymphocyte count, and CD8 lymphocyte count.

Echocardiographic evaluation, including M-mode, 2-dimensional, and Doppler echocardiographic studies, was done in all patients by a single experienced cardiologist using an Aloka SSD 870 ultrasound machine with a 3.5 MHz transducer. The echocardiographic evaluator was blinded to the patients' hematological and serological data at the time of examination. All echocardiographic measurements were double-checked by a second experienced cardiologist, who was also blinded to the patients' information. Measurements were made according to the recommendations of the American Society of Echocardiography,[23,24] with focus on LV systolic and diastolic functions. All of the clinical investigations described above were performed in accordance with the Declaration of Helsinki.

Left ventricular systolic function

Parasternal long-axis, short-axis, and apical 2-chamber and 4-chamber views were obtained. M-mode echocardiography was used to measure the diastolic dimensions of the left atrium (LA) and right ventricle (RV), the diastolic thickness of the interventricular septum (IVS) and left ventricular posterior wall (LVPW), and the left ventricular diastolic and systolic diameters (LVEDD and LVESD).

Left ventricular end-diastolic and end-systolic volumes (LVEDV and LVESV) were calculated according to the formula used by Teichholz et al.[25] Stroke volume (SV) and LV mass were also calculated accordingly. Stroke volume index (SVI) and LV mass index (LVMI) were the division of SV and LV mass by the body surface area.

Left ventricular fractional shortening (LVFS) and ejection fraction (LVEF) were also calculated. The global and segmental left ventricular wall motions were evaluated by 2-dimensional echocardiography from various echo views. Cardiac output (CO) was estimated by multiplying the SV with the heart rate. Cardiac index (CI) was defined as CO divided by the body surface area.

Left ventricular diastolic function

Left ventricular filling was recorded by pulsed-wave Doppler with the sample volume placed between the tips of mitral leaflets. Peak velocities of the early (E) and late (A) mitral inflow (cm/s), and deceleration time (DT, ms) of the E wave were measured. The E/A ratio and deceleration slope (DS, cm/s^2) of the E wave were also calculated.

The isovolumic relaxation time (IVRT, ms), defined as the time interval between the aortic valve closure and mitral valve opening, was measured from the components of the aortic valve closure sound to the beginning of mitral inflow using pulse-wave Doppler. The values were measured in 3 consecutive cardiac cycles and then averaged.

Statistical analysis

Comparisons of continuous data between 2 groups were analyzed with the unpaired, 2-tailed Student's *t* test. Categorical data in two by two contingency tables were analyzed with chi-squared test. The bivariate correlation method was applied to identify the relationship between CD4 lymphocyte count and LV systolic and diastolic functions.

Multiple regression analysis was employed for evaluating the predictive values of CD4 lymphocyte count and opportunistic infection for LV dysfunction after adjustment for other confounding factors. A value of $p < 0.05$ was considered statistically significant.

Results

During the study period, 98 patients (91 men and 7 women) aged 20 to 78 years (mean, 38.4 ± 12.6 years) were included. Sixty six cases were from outpatient clinics, while 32 were hospitalized patients. Fifty two patients (53.1%) had a CD4 lymphocyte count greater than 200/μL. Among the 46 patients with CD4 counts less than 200/μL (46.9%), 23 (23.5%) had clinically active opportunistic infections while 23 (23.5%) did not. The opportunistic infections included bacterial or fungal septicemia (5 cases), mycobacterium infection (15 cases; 6 pulmonary, 6 extra-pulmonary, and 3 disseminated), cytomegalovirus infection (5 cases), *Pneumocystis carinii* pneumonia (2 cases), cryptococcal infection (2 cases), and herpes simplex virus infection (1 case). Among these 23 patients, 7 had more than one kind of infection identified at the time of inclusion.

No significant differences were found between the patients with CD4 ≥ 200/μL and those with CD4 < 200/μL regarding age, gender, body height, diastolic blood pressure, and mean blood pressure (Table 1). Body weight and systolic blood pressure were higher in patients with CD4 ≥ 200/μL, while the heart rate was higher in patients with CD4 < 200/μL. The patients with CD4 ≥ 200/μL had higher hemoglobin concentration and more of them received zidovudine treatment; however, fewer of them were hospitalized. The mean CD8 count did not differ between patients with CD4 ≥ 200/μL and those with CD4 < 200/μL.

The LA dimension was smaller in patients with CD4 count < 200/μL, while the RV dimension was larger (Table 2). There were no significant differences in the dimensions of IVS, LVPW, LVEDD, LVESD, LVEDV, and LVESV. The LV mass showed a borderline significant difference between the 2 groups (157.8 ± 46.1 g for patients with CD4 ≥ 200/μL *vs* 141.8 ±

Table 1. Clinical characteristics of HIV-infected patients.

Variable	CD4 count ≥ 200/μL (n = 52)	CD4 count < 200/μL	
		Without opportunistic infections (n = 23)	With opportunistic infections (n = 23)
Age (years) [mean ± SEM]	38.9 ± 15.1	39.1 ± 10.0	36.3 ± 8.6
Men/total [n (%)]	46/52 (88.5)	23/23 (100)	22/23 (95.7)
Body weight (kg) [mean ± SEM]	61.7 ± 11.6†	55.9 ± 8.4	54.1 ± 12.0
Heart rate (/minute) [mean ± SEM]	72.3 ± 13.6‡	82.2 ± 10.7§	93.3 ± 16.8
Blood pressure (systolic/diastolic, mm Hg) [mean ± SEM]	116.4 ± 13.0*/70.3 ± 9.2	111.7 ± 11.9/71.4 ± 11.8	108.8 ± 11.6/67.5 ± 9.5
Mean blood pressure (mm Hg) [mean ± SEM]	85.7 ± 9.3	84.8 ± 10.5	81.2±8.5
CD4/CD8 (count/μL) [mean ± SEM]	586 ± 260‡/925 ± 423	83 ± 60/866 ± 479	56 ± 52/493 ± 308
Hemoglobin (mg/dL) [mean ± SEM]	14.3 ± 1.6‡	12.5 ± 2.4	11.4 ± 2.3
Hospitalization [n (%)]	4/52 (7.7)‡	323 (13.0)‖	23/23 (100)
Zidovudine treatment [n (%)]	39/51 (76.5)*	13/23 (56.5)	8/18 (44.4)

* $p < 0.05$, † $p < 0.01$, and ‡ $p < 0.001$ for CD4 ≥ 200/μL versus CD4 < 200/μL.
§ $p < 0.05$ and ‖ $p < 0.001$ for patients with versus those without opportunistic infections in the subgroup with CD4 < 200/μL.

Table 2. Echocardiographic and echo-Doppler characteristics of HIV-infected patients (mean ± SEM).

	CD4 count ≥ 200/μL (n = 52)	CD4 count < 200/μL	
		Without opportunistic infections (n = 23)	With opportunistic infections (n = 23)
Left atrium (mm)	32.0 ± 5.3†	29.2 ± 4.6	28.5 ± 7.4
Right ventricle (mm)	19.2 ± 4.6*	20.3 ± 4.6	22.3 ± 6.3
LV end-diastolic dimension (mm)	47.7 ± 4.3	46.2 ± 4.7	46.4 ± 5.7
LV end-diastolic volume (mL)	105.3 ± 24.2	99.8 ± 24.7	100.8 ± 28.3
LV mass (g)/LVMI (g/m²)	157.8 ± 46.1§/93.9 ± 26.8	146.8 ± 34.3/89.9 ± 15.6	136.7 ± 31.9/86.1 ± 16.0
SV (mL)/SVI (mL/m²)	68.8 ± 12.9†/41.2 ± 7.4*	60.9 ± 15.6/37.8 ± 7.3	59.1 ± 17.6/37.1 ± 10.8
CO (L/min)/CI (L/min/m²)	5.3 ± 1.5/3.2 ± 1.0	4.9 ± 1.2/3.1 ± 1.1	5.7 ± 1.9/3.6 ± 1.2
LV fractional shortening (%)	36.0 ± 5.4†	33.4 ± 6.4	31.4 ± 6.3
LV ejection fraction (%)	65.1 ± 7.3†	61.5 ± 9.3	59.3 ± 9.5
IVRT (ms)	107.1 ± 19.5‡	94.7 ± 18.5	87.9 ± 17.3
E wave/A wave (cm/s)	65.4 ± 17.6/44.4 ± 14.7	60.0 ± 12.5/45.7 ± 15.7	61.3 ± 13.3/50.6 ± 11.9
E/A ratio	1.7 ± 1.6	1.4 ± 0.5	1.2 ± 0.3
Deceleration time (ms)	182.1 ± 38.5	192.6 ± 56.0	187.7 ± 41.1
Deceleration slope (m/s²)	3.8 ± 1.4	3.4 ± 1.1	3.4 ± 1.0

* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$, and § $p = 0.05$ for CD4 ≥ 200/μl versus CD4 < 200/μL.
LV = left ventricular; LVMI = left ventricular mass index; SV = stroke volume; SVI = stroke volume index; CO = cardiac output; CI = cardiac index; IVRT = isovolumic relaxation time.

33.2 g for those with CD4 < 200/μL, $p = 0.050$). When the LV mass was divided by body surface area, however, no significant difference in LVMI was noted between the 2 groups.

For LV systolic function, LVFS, LVEF, SV, and SVI were all lower in patients with CD4 count < 200/μL. However, when estimating CO by multiplying the SV by heart rate, no significant differences were noted between the 2 groups. Cardiac index also did not differ significantly between the 2 groups. As to LV diastolic function, IVRT was longer in patients with CD4 ≥ 200/μL (107.1 ± 19.5 *vs* 90.9 ± 17.8 ms, $p < 0.001$). However, for other parameters such as E wave, A wave, E/A ratio, DT, and DS, no significant differences were noted between the 2 groups.

As several factors might potentially influence LV diastolic function,[26] patients with factors such as old age (> 60 years old), mitral regurgitation, aortic regurgitation, and pericardial effusion were excluded from further analysis. After restratification, 43 patients with CD4 ≥ 200/μL and 28 with CD4 < 200/μL were entered into the subanalysis, and the differences became significant for E wave (66.9 ± 18.0 *vs* 57.6 ± 11.6 cm/s, $p = 0.010$), DT (177.4 ± 37.6 *vs* 201.4 ± 50.8 ms, $p = 0.025$), and DS (4.0 ± 1.4 *vs* 3.1 ± 1.1 m/s^2, $p = 0.006$). The IVRT in patients with CD4 ≥ 200/μL was still longer than that in patients with CD4 < 200/μL (107.0 ± 20.7 *vs* 91.7 ± 18.5 ms, $p = 0.005$). Parameters of LV systolic function, such as LVFS, LVEF, SV, and SVI, were also significantly lower in patients with CD4 < 200/μL in this subanalysis.

In the patient group with CD4 count < 200/μL, those with opportunistic infections had higher heart rate and a greater frequency of hospitalization than those without (Table 1). With regard to the impact of opportunistic infections on LV function in patients with CD4 < 200/μL, no significant differences were noted between patients with and without opportunistic infection in any parameters of LV systolic and diastolic function (Table 2). This was also true in the subanalysis performed after excluding patients with factors possibly influencing the LV diastolic function as described above.

With the result that LV function was significantly lower in patients with decreased CD4 lymphocyte count, we further evaluated the relationship between these variables using the bivariate correlation method. The 2-tailed Pearson's correlation coefficient was 0.308 for CD4 and LVEF ($p = 0.002$), and 0.313 for CD4 and LVFS ($p = 0.002$), showing a positive correlation between CD4 lymphocyte count and LV systolic function. This positive correlation was also seen between CD4 count and IVRT (Pearson's correlation coefficient, 0.304; $p = 0.006$). In multiple regression analysis with forward selection recruiting all potential confounding factors — such as gender, age, body weight, blood pressure, heart rate, hemoglobin, CD4 lymphocyte count, and opportunistic infection, CD4 lymphocyte count was found to be the only significant factor that correlated with LVEF, LVFS, and IVRT, respectively (Table 3).

Table 3. Correlations between CD4 lymphocyte count and left ventricular systolic and diastolic functions in multiple regression analysis.

Variable	β	Standard error	*p*
LVEF	0.0081	0.003	0.003
LVFS	0.0059	0.002	0.002
IVRT	0.019	0.007	0.006

LVEF = left ventricular ejection fraction; LVFS = left ventricular fractional shortening; IVRT = isovolumic relaxation time.

Discussion

Myocardial dysfunction in HIV infection was previously regarded to be entirely a result of the poor general condition in patients with advanced HIV infection, or a result of myocardial involvement by opportunistic infections. However, evidence of LV systolic and diastolic dysfunction even in asymptomatic seropositive HIV carriers suggested a more complex association. Moreover, evidence of myocarditis in HIV-infected patients, and the detection of HIV nucleic acid sequences in the myocardial and interstitial dendritic cells by in situ hybridization early in the disease course[20,27–31] had led to increased emphasis of the intrinsic role of HIV itself in the cardiopathogenic process of the disease.

In this study, LV systolic function including LVFS, LVEF, SV, and SVI were significantly lower in HIV-infected patients with CD4 lymphocyte counts less than 200/μL, though the mean values in both groups were still in the normal ranges. This result was compatible with Cardoso et al's study in which comparison was made between AIDS patients and asymptomatic HIV-seropositives.[11] Furthermore, the positive correlation between LV systolic function and CD4 lymphocyte count also accorded with the results of Barbaro and Di Lorenzo, that demonstrated a significant correlation between LV fractional shortening and the number of CD4-positive cells.[21]

Nevertheless, when considering the overall cardiac performance such as the cardiac output and cardiac index, no significant differences could be detected. This might well be explained as the compensation of the lower stroke volume by the higher heart rate in patients with CD4 lymphocyte count less than 200/μL, resulting in no significant change to cardiac output and cardiac index.

As to LV diastolic function, IVRT has been the most commonly mentioned parameter that changes significantly in HIV-infected patients. Previous studies demonstrated that IVRT was prolonged in HIV-infected patients and in asymptomatic HIV carriers compared with normal controls.[9–11] However, no significant differences were found between symptomatic and asymptomatic,[9] or between AIDS and the AIDS-related complex groups.[11] In our study, IVRT in HIV-infected patients was significantly shorter when the CD4 lymphocyte counts was below 200/μL. The bivariate correlation analysis also showed a positive correlation between CD4 count and IVRT. This suggests that IVRT is progressively shortened with decreasing CD4 lymphocyte count as the disease advances, though it might be initially prolonged in the early asymptomatic stage of HIV infection.[9–11]

Since IVRT is prolonged with impaired LV relaxation and shortened with decreased LV compliance (increased LV stiffness),[26] our results in association with the findings in previous studies suggest a dynamic change in IVRT as the LV diastolic function evolves in the clinical course of HIV infection. In other words, active relaxation of the LV is first impaired, followed by decreased compliance and increased stiffness as the disease progresses.

Effects on other parameters of LV diastolic function, such as E wave, A wave, E/A ratio, deceleration slope, and early filling time-velocity integral in HIV infection have also been discussed in the literature. In a large-scale study comparing 1236 asymptomatic HIV-positive patients with healthy controls, Barbaro et al demonstrated a significant reduction in E/A ratio, early diastolic filling time-velocity integrals, and late diastolic filling time-velocity integrals in HIV-positive patients.[10] Coudray et al also showed that HIV-infected patients, both symptomatic and asymptomatic, have lower E wave velocity, decreased EF deceleration slope, and longer early filling flow duration compared with normal controls. However, when comparing symptomatic with asymptomatic HIV-positive patients, there were no significant differences in any of the diastolic function parameters.[9] In this study, LV diastolic functional parameters were not significantly different between the patients with CD4 count above and below 200/μL. After excluding factors possibly influencing LV diastolic function, however, the data revealed a lower E wave, longer deceleration time, and less steep deceleration slope in patients with CD4 lymphocyte count less than 200/μL. The IVRT was still significantly shorter. These results offer further evidence of progressive changes in diastolic function, manifesting mainly as an increase in LV stiffness as CD4 lymphocyte count decreases in the clinical course of HIV infection.

As the chances of opportunistic infection markedly increase when CD4 lymphocyte count falls below 200/μL, it is of interest whether the poorer LV systolic and diastolic function in patients with CD4 count less than 200/μL were confounded by the presence of opportunistic infections. In this study, no significant differences in LV systolic and diastolic functions were detected between the patients with and without opportunistic infections. This result remained unchanged when excluding factors possibly influencing LV diastolic function.

Furthermore, CD4 lymphocyte count was the only factor significantly correlated with LV systolic and diastolic dysfunction in multiple regression analysis, indicating that opportunistic infection had little, if any, influence on LV systolic and diastolic dysfunction in HIV-infected patients.

Ventricular diastolic dysfunction with preserved systolic function has been reported at the early stages of several cardiovascular diseases, such as hypertension, coronary artery disease, hypertrophic cardiomyopathy, and heart transplant rejection.[32] It is usually regarded as the first manifestation of these diseases. Similarly, the impairment of LV diastolic function in early HIV infection might indicate an initial state of myocardial involvement.[9]

As the disease progresses, the gradual deterioration in both LV systolic and diastolic function parallels the cardiomyopathic process of HIV infection in the heart, which is signified by the gradual decline in CD4 lymphocyte count observed clinically. Further pathological and immuno-cytochemical studies are mandatory for clarifying this pathophysiological hypothesis, especially the direct cardiopathogenic role of HIV itself.

In conclusion, LV diastolic dysfunction may occur early in the clinical course of HIV infection. As the disease progresses, LV systolic and diastolic function deteriorate gradually. Decrease in CD4 lymphocyte count bears a good correlation with the decline in LV function, which implicates the possible pathophysiological process underlying the HIV-related cardiomyopathy. In contrast, opportunistic infections, though regarded as a hallmark of advanced diseases, seem to play a limited role in the development of LV systolic and diastolic dysfunction in HIV infection.

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