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BRIEF REPORT

Acute HIV Infection Results in Subclinical Inflammatory Cardiomyopathy

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The impact of excess viral RNA on myocardial function and morphology in the setting of acute human immunodeficiency virus (HIV) infection remains unknown. In this study, 49 patients with acute HIV infection showed increased levels of N-terminal prohormone of brain natriuretic peptide, a surrogate of myocardial function, which decreased with viral suppression and normalization of systemic inflammation (79 pg/mL vs 28 pg/mL; $P < .001$). A comparable change was seen with levels of troponin T, a marker of morphologic myocardial damage (4.9 ng/L vs 1.5 ng/L; $P < .001$). In conclusion, we observed significant functional and morphological myocardial impairment during acute HIV infection, fueled by inflammatory activation and extensive viral replication, resulting in a reversible subclinical inflammatory cardiomyopathy.

Keywords. NT-proBNP; troponin T; myocardial function; myocardial damage; inflammation.

Acute human immunodeficiency virus (HIV) infection refers to a transient symptomatic illness showing uncontrolled viremia and widespread destruction of immune cells following HIV acquisition [1]. It is characterized by high plasma levels of HIV RNA in the absence of anti-HIV antibodies.

Many symptoms of acute HIV infection reflect the immune response to the virus, and most symptoms occur before or at the time of the peak viremia level, usually resolving quickly as the viral load decreases [2]. Concomitant with alterations in the composition of the lymphocyte compartment during acute HIV infection, uncontrolled viral replication is associated with a dramatic cytokine cascade displaying elevated levels of a plethora of cytokines, such as interferon α, interferon γ, interleukin 15, interleukin 6, interleukin 8, and tumor necrosis factor α [3]. This intense cytokine storm promotes immune activation aimed at controlling viral replication, but it also contributes to the early immunopathology, as well as to inflammation-associated short-term and long-term sequelae, among which cases of acute myopericarditis and dilated cardiomyopathy have been reported [4]. The exact underlying pathophysiologic mechanism of this myocardial involvement in the setting of acute HIV infection may involve direct cytopathic effects of HIV on the cardiomyocyte, inflammation-triggered myocardial depression, or concomitant viral coinfection. Recent data demonstrated that, in treatment-naive patients with chronic HIV infection and low $CD4^+$ T-cell counts, viral replication is associated with subclinical cardiac dysfunction evidenced by higher levels of NT-proBNP [5]. However, the impact of excess viral RNA on myocardial function and morphology in the extreme setting of acute HIV infection, with viral loads often exceeding 1 million copies/mL, remains unknown.

The vasoactive vascular hormone N-terminal prohormone of brain natriuretic peptide (NT-proBNP) has been introduced into clinical practice as a valuable laboratory surrogate for myocardial function, as well as a reliable predictor of mortality in various cardiovascular diseases [6]. Troponin T is part of the troponin complex expressed in the cardiomyocyte and is therefore a sensitive and specific biomarker for cardiomyocyte injury [7].

The objective of this study was to assess the impact of acute HIV infection on the heart, using functional (ie, NT-proBNP) and morphological (ie, troponin T) cardiac surrogates, and to determine whether these anticipated detrimental effects are related to inflammatory status.

METHODS

Study Population

We enrolled 49 patients with acute HIV infection at Vienna General Hospital, a university-affiliated tertiary care center, using a database search. All had a normal cardiac status (defined as no documented cardiac disease or no electrocardiographic abnormalities) and a normal renal status (defined as an estimated glomerular filtration rate >60 mL/minute). The study was reviewed and approved by the Ethics Committee of the Medical University of Vienna (ECS 1232/2017) and complies with the Declaration of Helsinki.

Data Acquisition

The patients' digital medical records at Vienna General Hospital were screened by trained chart reviewers and processed into a designed record abstraction form as previously reported [5]. Acute HIV infection was defined as (1) a positive HIV nucleic acid test result and a negative HIV antibody test result; (2) a

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positive HIV antibody test result ≤6 months after a negative HIV test result; (3) a positive HIV nucleic acid test result, with p24 antigen positivity and <4 positive bands on Western blot analysis; or (4) clinical manifestation of acute HIV infection, supported by p24 antigen positivity or positive HIV nucleic acid test result and <4 bands on Western blot analysis [8]. Cardiac status was considered to be normal in the absence of documented previous cardiac disease and clinically significant electrocardiographic abnormalities. Blood samples were routinely collected at every outpatient visit, and the NT-proBNP level was measured routinely at the first patient visit (eg, during acute HIV infection) and thereafter at least once yearly in a standardized, prospective manner. The troponin T level was analyzed in frozen samples according to the local laboratory's standard procedure.

For this study, laboratory measurements at the time of enrollment and at a follow-up visit after a median interval of 22 months (interquartile range [IQR], 12–42 months) of HIV viremia suppression (defined as an HIV RNA level <50 copies/mL; AmpliPrep, Roche, Switzerland) were used. Measurements of the NT-proBNP level (upper limit of normal, 125 pg/mL) and high-sensitivity troponin T level (upper limit of normal, 14 ng/L) were performed in heparin plasma, using the Elecsys Systems (Roche Diagnostics, Mannheim, Germany). All laboratory measurements were performed in an International Organization for Standardization–accredited facility (Department of Laboratory Medicine, Medical University of Vienna).

Statistical Methods

Continuous data are presented as median values and IQRs and were compared using Wilcoxon signed rank statistics. The Spearman correlation coefficient was used to assess the relationship between NT-proBNP and troponin T levels and the $CD4^+$ T-cell count, viral load, and laboratory parameters. Next, univariate linear regression was used to determine independent associations between the NT-proBNP level and baseline variables, and multivariate linear regression was performed to investigate the association between the NT-proBNP level and HIV-associated factors, as well as markers of inflammation and immune activation (ie, viral load, C-reactive protein, platelet count, serum amyloid A level, and lactate dehydrogenase [LDH] level). The same multivariate linear regression model was used to evaluate changes in these associations at a follow-up visit in which the viremia level was suppressed to a level below the limit of quantification. Two-sided *P* values of <.05 indicate statistical significance. Stata 14.2 (College Station, TX) was used for all analyses, and graphs were drawn with GraphPad Prism, version 5.03 (San Diego, CA).

RESULTS

Study Population

From March 2006 to December 2015, 49 patients with a diagnosis of acute HIV infection according to standardized criteria met the inclusion criteria and were included in our study. Detailed baseline characteristics of the patients at the time of diagnosis are presented in Table 1. The median age was 37 years (IQR, 29–45 years), and the majority of patients were white (92%), male (90%), and infected through homosexual intercourse (74%). The median $CD4^+$ T-cell count at diagnosis was 373 cells/μL (IQR, 273–579 cells/μL), and the median HIV load was 6.04 $\log_{10}$ copies/mL (IQR, 5.42–6.81 $\log_{10}$ copies/mL) (Table 2). Eighty percent of the patients presented with at least 1 symptom, of which fever was the commonest (49% of patients). Combination antiretroviral therapy (cART) was commenced in 84% of patients within 3 months after diagnosis. With respect to the classical cardiovascular risk factors,

Table 1. Baseline Characteristics of the Study Population During Acute Human Immunodeficiency Virus Infection

Variable	Value (n = 49)
Age, y	37 (29–45)
Male sex	44 (90)
White	45 (92)
Mode of transmission	
Male-male sex	36 (74)
Heterosexual sex	7 (14)
Injection drug use	5 (10)
Unknown	1 (2)
Clinical symptom at presentation	
Any	39 (80)
Fever	24 (49)
Rash	17 (35)
Pharyngitis	14 (29)
Lymphadenopathy	9 (18)
Other	18 (37)
cART use ≤3 mo after study entry	
Overall	41 (84)
NRTIs	
TDF + FTC	38 (93)
3TC + ABC	2 (5)
AZT + 3TC	1 (2)
Third agent	
NNRTI	6 (15)
PI	15 (36)
INI	20 (49)
ECG finding	
Sinus rhythm	49 (100)
PQ interval, s	0.16 (0.14–0.16)
QRS complex, s	0.08 (0.08–0.08)
QT interval, s	0.39 (0.37–0.4)
Comorbidity	
Active hepatitis B	1 (2)
Active hepatitis C	4 (8)
Diabetes	0 (0)
Hypertension	3 (6)
Cholesterol level, mg/dL	169 (149–206)
Smoker	25 (57)

Data are no. (%) of participants or median values (interquartile ranges).

Abbreviations: ABC, abacavir; AZT, zidovudine; cART, combination antiretroviral therapy; ECG, electrocardiography; FTC, emtricitabine; INI, integrase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

6% had mild hypertension, 31% had hypercholesterolemia, 0% had diabetes, and 57% were current smokers.

Myocardial Involvement and Inflammatory Response in Acute HIV Infection

During acute HIV infection, 32.7% of patients showed elevated levels of NT-proBNP, with median levels of 79 pg/mL (IQR, 33–179 pg/mL), compared with 28 pg/mL (IQR, 10–39 pg/mL) after suppression of viremia below the limit of quantification ($P < .001$; Figure 1 and Table 2). The NT-proBNP level showed a significant correlation with the absolute $CD4^+$ T-cell count (r = 0.29; $P = .044$) and viral load (r = 0.48; $P < .001$). Concomitantly, the troponin T level, a surrogate of morphologic myocardial cell injury, was elevated in 22.4% of the patients, with median levels of 4.9 ng/L (IQR, 2.9–12.8 ng/L) during acute HIV infection and 1.5 ng/L (IQR, 1.5–3.9 ng/L) after attainment of a plasma HIV-1 RNA load below the limit of quantification ($P < .001$). The troponin T level also showed a significant correlation with viral load (r = 0.44; $P = .001$) but no correlation with the absolute $CD4^+$ T-cell count (r = 0.12; $P = .39$).

In a multivariate linear regression model, NT-proBNP levels at the time of diagnosis of acute HIV infection were dependent on a composite of HIV load, as well as humoral and cellular inflammatory activation markers (C-reactive protein level, serum amyloid A level, platelet count, and LDH level), resulting in an overall fit (ie, R^2) of 0.65 ($P < .001$). By using the same model, after attainment of viral suppression this association between the NT-proBNP level and the aforementioned parameters vanished ($R^2 = 0.09$; $P = .545$). In univariate analyses, interleukin 6 levels, $HLA\text{-}DR^+CD3^+$ T-cell counts, and leukocyte counts, as well as sex, age, or traditional cardiovascular risk factors, were not significant predictors of the NT-proBNP level at baseline.

Discussion

In this study, we investigated the impact of acute HIV infection on the heart, demonstrating that acute HIV infection with its excessive viral replication and concomitant inflammatory reaction leads not only to subclinical myocardial dysfunction but also to direct myocardial damage. It has previously been shown that, in treatment-naive patients with a low $CD4^+$ T-cell count and a high HIV load, elevated levels of NT-proBNP are observed, hinting at a subclinical impact of HIV infection on myocardial function [5]. To date, it is not known whether there is also concomitant structural cardiac damage related to chronic HIV infection. Acute HIV infection most likely represents the ideal setting to investigate the impact of HIV on myocardial function and morphology, given the excess viral RNA and concomitant inflammatory response usually not encountered in other stages of HIV infection. It has been hypothesized that immune activation and chronic inflammation represent the major contributors to cardiovascular risk development in HIV-infected individuals and that even successful treatment with antiretrovirals exhibiting little metabolic side effects is unable to completely abrogate this phenomenon [9, 10]. Consequently, it is tempting to speculate that the cornerstone of progressive myocardial damage occurs during acute HIV infection. Indeed, we showed that almost a quarter of patients with acute HIV infection have increased troponin T levels, a direct marker of myocardial damage, without any cardiac symptoms.

Of interest, our finding that, after suppression of viremia, levels of both troponin T and NT-proBNP were significantly reduced implies that the combination of high-level viremia, immunodeficiency (defined as a decreased $CD4^+$ T-cell count), and immune activation plays a central role in the development of an acute HIV infection–induced inflammatory cardiomyopathy, reflected by subclinical impairment of myocardial function (for which the NT-proBNP level is a surrogate) and morphologic myocardial damage (for which the troponin T level is a surrogate). This notion is further underlined by our regression model displaying that C-reactive protein, serum amyloid A, and LDH levels, as well as the platelet count, reflect the NT-proBNP level. Moreover, the significance of myocardial inflammation during HIV infection is further supported by cardiac magnetic resonance imaging studies that demonstrate a high incidence of fibrosis, early gadolinium enhancement, and myocardial edema even in asymptomatic HIV-infected patients receiving cART [11, 12].

Of note, our observation that myocardial damage in HIV-infected individuals is primarily observed during the acute HIV infection supports the notion that myocardial fibrosis develops after cell injury or death, which predominates during acute rather than chronic infection [13]. However, not all inflammatory biomarkers are useful for predicting the NT-proBNP level. Interleukin 6 levels, leukocyte counts, and heightened T-cell activation, identified as the proportion of $CD3^+$ T cells that expressed HLA-DR, did not show a significant association, perhaps indicating that specific inflammatory pathways are involved in damaging the myocardium. Of note, in contrast to findings from an earlier study [5], the $CD4^+$ T-cell count during acute HIV infection is positively correlated with the NT-proBNP level but is not statistically significantly correlated with the viral load

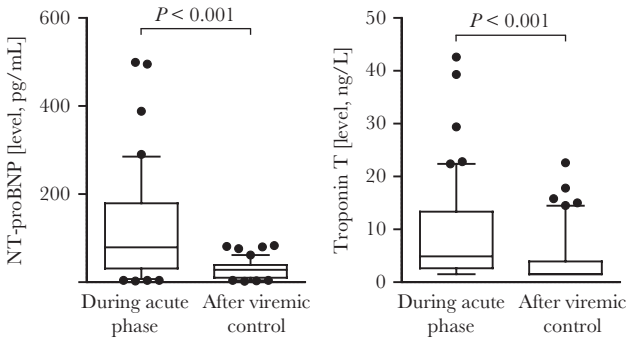

Figure 1. Box plots with medians, interquartile ranges, interdecile ranges, and outliers for N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and troponin T levels at the time of acute human immunodeficiency virus infection and after attainment of viremic control (defined as a viral load below limit of quantification [ie, <50 copies/mL]).

Table 2. Comparison of Laboratory Parameters During the Acute Phase of Human Immunodeficiency Virus (HIV) Infection and After Viremic Control

Parameter	During Acute Phase	After Viremic Control[a]	*P*
$CD4^+$ T-cell count, cells/μL	373 (273–579)	625 (478–893)	<.001
HIV load, copies/mL	6.04 (5.42–6.81)	1.29 (1.29–1.3)	<.001
NT-proBNP level, pg/mL	79 (33–179)	28 (10–39)	<.001
Troponin T level, ng/L	4.9 (2.9–12.8)	1.5 (1.5–3.9)	<.001
CRP level, mg/dL	0.27 (0.09–0.83)	0.15 (0.06–0.29)	.002
SAA level, μg/mL	3.9 (3.9–4.9)	3.9 (3.9–3.9)	.002
IL-6 level, pg/mL	7 (7–7)	7 (7–7)	.06
$HLA\text{-}DR^+CD3^+$ T cells, %	31 (24–42)	9 (7–12)	<.001
Leukocyte count, G/L	5.3 (4.3–6.4)	6.0 (4.8–7.9)	.104
Hemoglobin level, g/dL	14.4 (13.6–15.3)	15.3 (14.2–15.7)	.002
Platelet count, ×1000 platelets/μL	192 (156–229)	225 (180–239)	.022
Estimated GFR, mL/min/1.73 m^2	94 (86–107)	81 (73–94)	<.001
Blood urea nitrogen level, mg/mL	10.6 (9.2–12.9)	12.3 (10.9–15.4)	.005
LDH level, U/L	211 (187–247)	177 (166–198)	<.001
Bilirubin level, mg/dL	0.54 (0.43–0.72)	0.44 (0.34–0.65)	.78
Cholinesterase level, U/L	7540 (6220–8760)	8410 (7020–9600)	<.001
GGT level, U/L	34 (23–53)	23 (15–37)	.008
AST level, U/L	30 (24–39)	29 (22–32)	.0103
ALT level, U/L	29 (21–51)	25 (19–36)	.017

Data are median values (interquartile ranges) for 49 study participants.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; GFR, glomerular filtration rate; GGT, γ-glutamyltransferase; IL-6, interleukin 6; LDH, lactate dehydrogenase; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; SAA, serum amyloid A.

[a]Defined as an HIV load below the limit of quantification (ie, <50 copies/mL)

or C-reactive protein level. A possible explanation of this finding is that the $CD4^+$ T-cell count usually drops during acute HIV infection without reflecting the increasing immunodeficiency observed during chronic HIV infection.

It can be speculated that a similar decline in the NT-proBNP and troponin T levels can be observed in elite controllers after abatement of acute HIV infection. However, in most patients without access to cART, chronic low-level replication and immune activation might represent the basis for the development of future cardiovascular disease, including the occurrence of overt HIV cardiomyopathy [14]. Nevertheless, future longitudinal studies could clarify whether an elevated troponin T level during acute HIV infection reflects irreversible myocardial death and translates to a reduction of left ventricular function, as present in overt HIV cardiomyopathy, or to a higher rate of cardiac events, similar to what has been described in HIV-negative patients with elevated troponin T levels [15]. In any case, relying on our results and previous investigations, it is tempting to speculate whether patients with elevated levels of troponin T and NT-proBNP during acute HIV infection represent a subgroup at increased risk for future cardiovascular events who might therefore benefit from intensified clinical monitoring and initiation of cART at the earliest time point possible [5].

To the best of our knowledge, this is the first study investigating the impact of HIV on the heart during acute HIV infection. Taken together, our findings confirm functional and morphologic myocardial impairment during acute HIV infection fueled by both humoral and cellular inflammatory activation, as well as massive viral replication, resulting in an early stage subclinical inflammatory cardiomyopathy.

Note

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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