Impact of HIV Infection on Diastolic Function and Left Ventricular Mass

Priscilla Y. Hsue, MD; Peter W. Hunt, MD; Jennifer E. Ho, MD; Husam H. Farah, MD; Amanda Schnell, BA; Rebecca Hoh, RD; Jeffrey N. Martin, MD, MPH; Steven G. Deeks, MD; Ann F. Bolger, MD

Background—Patients with HIV have increased risk for cardiovascular disease, but the underlying mechanisms remain unknown. The purpose of this study was to determine the prevalence of echocardiographic abnormalities among asymptomatic HIV-infected individuals compared with HIV-uninfected individuals.

Methods/Results—We performed echocardiography in 196 HIV-infected adults and 52 controls. Left ventricular ejection fraction, left ventricular mass indexed to the body surface area, and diastolic function were assessed according to American Society of Echocardiography standards. Left ventricular mass index was higher in HIV-infected patients (77.2 g/m² in patients with HIV versus 66.5 g/m² in controls, P<0.0001). Left ventricular ejection fraction was similar in both groups. Eight (4%) of the patients with HIV had evidence of left ventricular systolic dysfunction (defined as an EF <50%) versus none of the controls; 97 (50%) had mild diastolic dysfunction compared with 29% of the HIV-uninfected subjects (P=0.008). After adjustment for hypertension and race, HIV-infected participants had a mean 8 g/m² larger left ventricular mass index compared with controls (P=0.001). Higher left ventricular mass index was independently associated with lower nadir CD4 T-cell count, suggesting that immunodeficiency may play a role in this process. After adjustment for age and traditional risk factors, patients with HIV had a 2.4 greater odds of having diastolic dysfunction as compared with controls (P=0.019).

Conclusions—HIV-infected patients had a higher prevalence of diastolic dysfunction and higher left ventricular mass index compared with controls. These differences were not readily explained by differences in traditional risk factors and were independently associated with HIV infection. These results suggest that contemporary asymptomatic patients with HIV manifest mild functional and morphological cardiac abnormalities, which are independently associated with HIV infection. (Circ Heart Fail. 2010;3:132-139.)

Key Words: AIDS ■ diastole ■ echocardiography ■ hypertrophy ■ inflammation ■ heart failure

A ntiretroviral medication has changed the spectrum of HIV infection from a fatal condition to a long term, chronic health condition. According to data from the Centers for Disease Control and Prevention, by the year 2015, 50% of patients with HIV will be older than the 50 years. Chronic health conditions such as cardiovascular disease will become increasingly important in this growing group of older individuals. In asymptomatic patients without HIV infection, echocardiographic abnormalities such as diastolic dysfunction as assessed by decreased mitral inflow E/A ratio and increased left ventricular mass have been associated with all-cause mortality.1 In children with HIV, mild depression of LV systolic function and elevated LV mass were associated with increased all-cause mortality.2 Previous studies of cardiac abnormalities in patients with HIV before the antiretroviral era demonstrated a high prevalence of dilated cardiomyopathy and pericardial effusion.3,4 There have been relatively few studies addressing cardiac abnormalities detectable by echocardiography among adults in the modern era. A study of HIV-infected black men who were cocaine users demonstrated that individuals taking protease inhibitors had higher interventricular septal thickness, higher left ven-

Clinical Perspective on p 139

tricular posterior wall thickness, and decreased E/A ratio.5 Recently, in a study of 30 HIV-infected men and uninfected controls, patients with HIV were found to have a higher prevalence of diastolic dysfunction, lower calculated ejection fraction, and higher pulmonary artery pressure compared with uninfected controls.6 As only treated patients were included,
the role of antiretroviral therapy including protease inhibitors could not be assessed independently of HIV infection.

The purpose of our study was to determine the prevalence of echocardiographic abnormalities among asymptomatic HIV-infected individuals compared with uninfected controls and to ascertain the independent contributions of HIV infection, detectable viremia, and antiretroviral therapy to those findings.

Methods

Participants
We recruited individuals with HIV infection from a large clinic-based cohort at San Francisco General Hospital (Study of the Consequences of the Protease Inhibitor Era). This cohort includes (1) untreated patients, defined as no antiretroviral therapy in the preceding 6 months; (2) treated patients with detectable viremia, defined as >24 weeks antiretroviral therapy with the most recent 2 HIV RNA levels >75 copies/mL; and (3) treated patients who achieved full viral suppression defined as >24 weeks antiretroviral therapy with 2 most recent HIV RNA levels <75 copies/mL. All participants were documented to be HIV-infected either by medical records, letter of diagnosis, or HIV-antibody testing. Participants were consecutive volunteers from the SCOPE study; the only inclusion criterion was HIV infection, and there were no other inclusion or exclusion criteria related to cardiovascular disease or traditional cardiovascular risk factors. For the uninfected control group, participants were persons who responded to advertisements for enrollment in clinical research studies directed toward persons believed to be HIV-uninfected. We targeted our enrollment of controls to individuals of similar age, gender, and smoking status to our HIV-infected population. All persons in this group were tested and documented to be HIV-antibody-negative before enrollment in the study. All participants provided written informed consent; the study was approved by the UCSF Committee on Human Research.

Measurements

Clinical and Sociodemographic Characteristics
We conducted a detailed interview with all study participants, which included information on traditional cardiovascular risk factors, medication use, sociodemographic features, and activity tolerance using the New York Heart Association classification. Hypertension, diabetes mellitus, and hyperlipidemia were defined by patient self-report and verified by chart review or were defined by being currently treated with medications for blood pressure, diabetes, or hyperlipidemia. Confidential self-administered questionnaires were used to ascertain the use of illicit drugs, including heroin, cocaine and amphetamine/methamphetamine, and a history of their intravenous usage, opportunistic infections, and nadir CD4 count.

Echocardiography
A single sonographer who was blinded to each participant’s HIV status and clinical characteristics performed all of the echocardiographic studies. We determined the presence of diastolic dysfunction according to guidelines from the American Society of Echocardiography (ASE). Using a Vivid 7 Imaging System (GE, Milwaukee, Wis), diastolic dysfunction was assessed using spectral Doppler mitral and pulmonary venous inflow velocity patterns and Doppler tissue imaging of the lateral mitral annulus. Three consecutive cardiac cycles were assessed and averaged for Doppler measurements. Stage 1 diastolic dysfunction was defined as impaired relaxation. Stage 2 diastolic dysfunction was defined as a pseudonormal filling pattern. Stage 3 diastolic dysfunction was defined as a restrictive filling pattern and evidence of reversibility with Valsalva maneuver. Finally, stage 4 was defined as a restrictive filling pattern without reversibility with Valsalva. Left ventricular end-diastolic and end-systolic volumes, ejection fraction, and left atrial volumes were assessed using the modified Simpson’s rule, and indexed to body surface area. Left ventricular mass was measured from midventricular short axis slice and long axis measured from the apical 4 chamber view; LV mass was indexed to body surface area. Reference limits from the American Society of Echocardiography were used to determine left ventricular hypertrophy for both men and women. Tricuspid regurgitation was assessed in 3 different views, and 3 sequential complexes were recorded. Continuous-wave Doppler measurement of the peak regurgitant jet velocity from any view was used to estimate the systolic pressure gradient between the right ventricle and the right atrium using the modified Bernoulli equation. Pulmonary artery systolic pressure was quantified by adding the calculated pressure gradient to the mean right atrial pressure, which was estimated from the diameter of the inferior vena cava, degree of inspiratory collapse, and hepatic vein Doppler profile using ranges from 0 to 5, 5 to 10, 10 to 15, 15 to 20, and >20 mm Hg. The severity of mitral regurgitation was assessed as grade 1 to 4 using standard echocardiographic criteria. All calculations and interpretations were performed off-line by 2 cardiologists (JEH and HHF) who were blinded to participants’ HIV infection and clinical status.

Laboratory Assays
The Triage B-Type Natriuretic Peptide Test (Biosite Inc, San Diego, CA) was used to measure B-type natriuretic peptide (BNP). Hepatitis C virus (HCV) serostatus was determined by the HCV EIA version 2.0 (Abbott Laboratories, Abbott Park, Ill). The nadir CD4+ T-cell count was the lowest laboratory-confirmed value before the echocardiography date. High sensitivity C-reactive protein was measured using the Dade Behring assay.

Statistical Analyses
For continuous variables, unadjusted comparisons between groups were made using Kruskal-Wallis test and then pairwise Wilcoxon rank sum tests; for categorical variables, χ² and Fisher exact tests were used. The Spearman rank correlation coefficients were used to assess correlations between continuous variables. Linear and logistic regressions were used to assess adjusted differences between groups. Continuous variables were transformed, and standard errors were calculated using heteroskedasticity-consistent covariance matrix estimators to satisfy model assumptions when needed. Age, gender, race, history of injection drug use, amphetamine, or cocaine use (ever versus never used), current cigarette use, and the diagnoses of hypertension, diabetes mellitus, hyperlipidemia, and hepatitis C virus infection were all considered as potential confounders. Potential confounders that were associated with the outcome of interest (in our study, diastolic dysfunction or higher left ventricular mass index) at the P<0.10 level in unadjusted analyses were assessed in multivariate models but then removed in a stepwise manner if their inclusion changed the β coefficient of the primary predictor by <10%. Sensitivity analyses were also performed restricting the analysis to those patients who reported never using amphetamines or cocaine or who did not have a history of hypertension.

Sample size estimates for differences in means and proportions between groups were estimated with the sampsi command in Stata version 10.0. To determine the number of patients for our study, we based our sample size calculation on a previous study of 30 HIV-infected patients and 26 uninfected controls which showed a higher prevalence of LV diastolic dysfunction in 64% of patients versus 12% of controls. Because we were recruiting a larger number of HIV-infected participants receiving antiretroviral therapy and an older control population enriched for smokers, we assumed that the difference in prevalence of diastolic dysfunction between HIV-infected participants and uninfected controls might be as small as 40% versus 20%. Assuming a type I error rate of 5%, we would have 80% power to detect a difference this small between groups by enrolling 196 HIV-infected individuals and 52 uninfected controls. We oversampled HIV-infected participants so that we could examine the relationship between antiretroviral therapy treatment status and presence of detectable viremia on left ventricular mass index. Although underpowered to detect differences in the presence of diastolic dysfunction by treatment status or presence of detectable viremia, with 168 treated and 28 untreated HIV-infected participants
and 128 with undetectable versus 68 with detectable viremia, a type I error rate of 5%, an SD in left ventricular mass index of 17 g/m²; we had 80% power to detect a difference between treated and untreated participants as small as 10 g/m² and a difference between those with and without detectable viremia as small as 7 g/m².

Results

Participant Characteristics

As shown in Table 1, 196 HIV-infected and 52 uninfected controls were studied. More than 80% of participants in both groups were men. The median age was 47 years in the HIV-infected group and 45 years in the uninfected controls. Most patients with HIV and controls were white; there was a higher percentage of black individuals in the HIV-infected group (25 versus 8%). Thirty-six percent of the patients with HIV were current smokers compared with 26% of the uninfected controls (P=0.13). The rates of intravenous drug use (IVDU) and methamphetamine use were higher in the HIV-infected patients (Table 1). More of the patients with HIV had a history of hypertension compared with uninfected controls (26% versus 6%) and similarly, more of the patients with HIV were on antihypertensive medications compared with uninfected controls (21% versus 4%). However, the average systolic blood pressure was similar in the patients with HIV and uninfected controls (122.4 mm Hg versus 122.6 mm Hg, respectively, P=0.92) as was the average diastolic blood pressure (77.0 mm Hg in the patients with HIV versus 77.8 mm Hg in the uninfected controls, P=0.63). Rates of diabetes mellitus, previous coronary artery disease, and hyperlipidemia were low and similar between the groups. Only 7 (2.8%) of all participants experienced class II or higher New York Heart Association activity tolerance, and all were class II.

Among the HIV-infected participants, the median duration of HIV diagnosis was 15 years, and 82% were currently using antiretroviral medication, whereas only 8% were treatment naïve. Among the subset being currently treated, the median duration of protease inhibitor use was 5.3 years, the median duration of nucleoside reverse transcriptase inhibitors was 7.9 years, and 63% percent had an undetectable viral load. Among all HIV-infected participants, the median CD4⁺ T-cell count was 420 cells/mm³, and the median CD4⁺ T-cell nadir was 120 cells/mm³.

Echocardiographic Findings

Baseline echocardiographic parameters are summarized by HIV status in Table 2. The median ejection fraction was similar in HIV-infected individuals (median 63%, interquartile range [IQR] 59 to 67) and uninfected controls (median 62%, IQR 59 to 67, P=0.63). Eight (4%) of the patients with HIV had an ejection fraction <50% (range 33% to 49%), whereas none of the controls had an ejection fraction <50% (P=0.21). Left atrial volume indices were higher in HIV-infected participants (median 26, IQR 21 to 30) compared with uninfected controls (median 20, IQR 16 to 25, P<0.001). Seven HIV-infected participants (4%) and 1 uninfected control (2%) had grade 2 mitral regurgitation (P=0.55); no subject had grade 3 mitral regurgitation. As we have previously reported,¹⁸ the median pulmonary artery systolic pressure among the HIV-infected participants was higher (median 27.5 mm Hg, IQR 22 to 32.5) than the uninfected controls (median 22 mm Hg, IQR 18 to 25; P<0.001, Wilcoxon rank sum). The median right atrial pressure was 5 mm Hg in both patients with HIV and controls. Using American Society of Echocardiography criteria,¹² 7 patients (4%) with HIV had evidence of left ventricular hypertrophy as compared with 1 uninfected control (2%; P=0.55).

Table 1. Characteristics of HIV-Infected Study Participants and Uninfected Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV-Infected (n=196)</th>
<th>HIV-Uninfected (n=52)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, median (IQR)</td>
<td>47 (42 to 52)</td>
<td>45 (40 to 56)</td>
<td>0.81</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>167 (85)</td>
<td>46 (89)</td>
<td>0.66</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>109 (54)</td>
<td>35 (67)</td>
<td>0.002</td>
</tr>
<tr>
<td>Black</td>
<td>51 (25)</td>
<td>4 (8)</td>
<td></td>
</tr>
<tr>
<td>Latino</td>
<td>13 (10)</td>
<td>5 (10)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>23 (11)</td>
<td>8 (15)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>50 (26)</td>
<td>3 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>9 (5)</td>
<td>4 (8)</td>
<td>0.48</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>64 (33)</td>
<td>13 (25)</td>
<td>0.32</td>
</tr>
<tr>
<td>Prior coronary artery disease</td>
<td>9 (5)</td>
<td>0 (0)</td>
<td>0.21</td>
</tr>
<tr>
<td>Injection drug use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever, but not current</td>
<td>74 (38)</td>
<td>1 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current</td>
<td>9 (5)</td>
<td>0 (0)</td>
<td>0.21</td>
</tr>
<tr>
<td>Amphetamines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever use</td>
<td>75 (38)</td>
<td>3 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever use</td>
<td>44 (22)</td>
<td>6 (12)</td>
<td>0.12</td>
</tr>
<tr>
<td>Current cigarette smoking</td>
<td>71 (36)</td>
<td>13 (26)</td>
<td>0.13</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>48 (25)</td>
<td>1 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of HIV infection (self-report) in years, median (IQR)</td>
<td>15 (11 to 18)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Use of antiretroviral medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever but not current</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRTI use duration in years, median (IQR)</td>
<td>7.9 (3.9 to 10)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>NNRTI use duration in years, median (IQR)</td>
<td>0.3 (0 to 3.4)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>PI use duration in years, median (IQR)</td>
<td>5.3 (0.96 to 7.7)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>CD4⁺ T cells/mm³, median (IQR)</td>
<td>420 (231 to 634)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>79 (41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadir CD4⁺ T cells/mm³, median (IQR)</td>
<td>120 (40 to 232)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Plasma HIV RNA copies/mL, % &lt;75</td>
<td>63</td>
<td>...</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as n (%).

NNRTI indicates nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.
Association Between HIV Infection and Diastolic Dysfunction

Ninety-seven (49%) HIV-infected participants had evidence of diastolic dysfunction compared with only 15 (29%) uninfected controls ($P=0.008$). In 6 patients with HIV, diastolic dysfunction could not be assessed (1 due to atrial fibrillation and 5 due to fusion of the E and A waves). In general, HIV-infected participants had lower E/A ratios and longer deceleration times on spectral Doppler assessment of mitral valve inflow when compared with uninfected controls ($P=0.03$ for both parameters). Tissue Doppler imaging revealed significantly lower mitral annular E’ velocities in HIV-infected compared with uninfected controls ($P<0.001$). Almost all of the diastolic dysfunction was stage 1; only 2 HIV-infected individuals had stage 2 diastolic dysfunction. In unadjusted analyses including all study participants, diastolic dysfunction was associated with older age ($P<0.001$) and hypertension ($P=0.002$). There was no evidence for an association between diastolic dysfunction and gender, diabetes mellitus, previous CAD, current cigarette smoking, hepatitis C virus infection, injection drug use (current or ever), amphetamine or cocaine use (current or ever), or race ($P>0.10$). After adjustment for age and hypertension, individuals with HIV infection had a 2.4-fold greater odds of having diastolic dysfunction compared with uninfected individuals ($P=0.019$) (Table 3). After restricting the analysis to participants who did not have hypertension, HIV-infected individuals still had a 2.4 increased risk for diastolic dysfunction ($P=0.024$) even after adjusting for age. Similarly, when restricting the analysis to participants reporting never to have used amphetamines or cocaine, HIV infection was independently associated with a higher risk of diastolic dysfunction in both unadjusted analysis ($P=0.01$) and analyses adjusted for age and hypertension ($P=0.048$).

Compared with those without diastolic dysfunction, HIV-infected participants with diastolic dysfunction had lower current CD4 T-cell counts (median 380 versus 460 cells/mm$^3$, $P=0.054$) and a longer duration of nucleoside reverse transcriptase inhibitor (NRTI) use (8.4 versus 6.9 years, $P=0.005$). However, after adjustment for age and hypertension, these associations were no longer significant ($P>0.17$ for each). There was no evidence for a relationship between diastolic dysfunction and current plasma HIV RNA level or duration of either protease inhibitor or nonnucleoside reverse transcriptase inhibitor use ($P>0.14$ for all).

We also compared the antiretroviral-treated subset (n=168) with the HIV uninfected subjects and found the same inferences. Of the 168 treated subjects, 84 had evidence of diastolic dysfunction, which was significantly higher than the HIV uninfected group ($P=0.007$). These differences remained significant after controlling for age and hypertension ($P=0.018$). Among the treated patients, a longer duration of NRTI use was associated with diastolic dysfunction ($P=0.002$) but again this was not significant after adjusting for age and hypertension ($P=0.10$).

Association Between HIV Infection and Elevated LV Mass Index

Overall, the LV mass index was significantly higher among individuals with HIV as compared with uninfected controls (77.2 g/m$^2$ versus 66.5 g/m$^2$, $P=0.0001$). Among all study participants, a higher LV mass index was associated with older age ($P=0.03$), male gender ($P=0.001$), and hypertension ($P=0.007$). Self-identified Latino race (compared with all other racial groups, $P=0.017$) was associated lower LV mass index. There was no evidence for a relationship between left ventricular mass index and hyperlipidemia, current cigarette smoking, injection drug use (current or previous use), or previous CAD in unadjusted analyses (all $P>0.20$). After adjustment for hypertension and Latino race, HIV-infected individuals had a mean 8 g/m$^2$ higher LV mass index than uninfected controls, $P=0.001$ (Table 4). Even when restricting the analysis to participants reporting never to have used amphetamines or cocaine, HIV

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Table 2. Baseline Doppler and Echocardiographic Parameters by HIV Status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HIV Positive (n=196)</th>
<th>Uninfected Controls (n=52)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic volume index, mL/m$^2$ (IQQR)</td>
<td>44 (36 to 51)</td>
<td>39 (34 to 49)</td>
<td>0.02</td>
</tr>
<tr>
<td>LV end-systolic volume index, mL/m$^2$</td>
<td>16 (13 to 20)</td>
<td>16 (13 to 19)</td>
<td>0.19</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>63 (59 to 67)</td>
<td>62 (59 to 67)</td>
<td>0.63</td>
</tr>
<tr>
<td>LV mass index, g/m$^2$</td>
<td>77 (65 to 89)</td>
<td>67 (63 to 73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LA volume index, mL/m$^2$</td>
<td>26 (21 to 30)</td>
<td>20 (16 to 25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PV systolic pressure, mm Hg</td>
<td>28 (22 to 33)</td>
<td>22 (18 to 25)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Baseline group differences assessed by Wilcoxon rank sum test.

LV indicates left ventricular; LA, left atrium; PA, pulmonary arterial; MV, mitral valve; PV, pulmonary vein; TDI, tissue Doppler imaging.

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Table 3. Unadjusted and Adjusted Odds of Diastolic Dysfunction in HIV-Infected and -Uninfected Controls

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>$P$</th>
<th>Odds Ratio (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uninfected control</td>
<td>Reference group</td>
<td></td>
<td>Reference group</td>
<td></td>
</tr>
<tr>
<td>HIV infected</td>
<td>2.4 (1.2 to 4.7)</td>
<td>0.009</td>
<td>2.4 (1.2 to 5.0)</td>
<td>0.019</td>
</tr>
<tr>
<td>Age per 10 year increase</td>
<td>2.4 (1.7 to 3.4)</td>
<td>&lt;0.001</td>
<td>2.5 (1.7 to 3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.7 (1.4 to 5.0)</td>
<td>0.002</td>
<td>2.3 (1.2 to 4.5)</td>
<td>0.016</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.6 (0.9 to 2.8)</td>
<td>0.087</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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infection continued to be independently associated with higher LV mass index in both unadjusted \((P=0.009)\) and adjusted analyses \((P=0.008)\). LV mass index values exceeded the gender-specific normal range in 4% of HIV-infected subjects and 2% of uninfected controls \((P=0.55)\).

Among HIV-infected individuals, lower self-reported nadir CD4 cell count was borderline associated with a higher LV mass index \((\text{Spearman rho} -0.14, P=0.052; \text{Figure})\). Even after adjustment for gender and hypertension, each 100 cell/mm\(^3\) decrease in self-reported nadir CD4\(^+\) T-cell count was associated with a mean 1.3 g greater LV mass \((P=0.013)\). There was no evidence for a relationship between LV mass index and either current CD4\(^+\) T-cell count or plasma HIV RNA level \((P>0.13\) for both). While a longer duration of NRTI use was associated with higher LV mass index in unadjusted analyses \((\text{Spearman rho} 0.15, P=0.037)\), the relationship was not significant after adjustment for nadir CD4\(^+\) T-cell count \((P>0.14)\). Neither duration of nonnucleoside reverse transcriptase inhibitor nor protease inhibitor use was associated with LV mass index.

We also compared the antiretroviral-treated subset \((n=168)\) with the uninfected controls and found similar results. The LV mass was higher in the treated subjects than the uninfected controls \((P<0.001)\). These differences remained significant after controlling for hypertension and Latino race \((P=0.001)\). Among the treated patients, there was no evidence for a relationship between current CD4 count, nadir CD4 count, viral load, or duration of antiretroviral therapy and LV mass index \((P>0.10\) for all).

Although the HIV-infected group was significantly enriched for black individuals relative to the uninfected controls, among all participants, there was no evidence for a relationship between black race and diastolic dysfunction \((P=0.74)\) or LV mass index \((P=0.23)\). Thus, the enrichment of blacks in the HIV-infected group is unlikely to confound the observed differences in diastolic dysfunction and LV mass index between the groups.

### Relationship Among B-Type Natriuretic Peptide, High sensitivity C-Reactive Protein, and Echocardiographic Findings

Plasma BNP levels were available on 227 participants; the median level was 5 pg/mL \((\text{IQR 2 to 12})\). The BNP levels were significantly higher among the HIV-infected patients \((6 \text{ pg/mL versus 3 pg/mL, } P=0.002)\) and higher BNP was associated with a higher LV mass index \((P=0.005)\). There was no association between BNP and diastolic dysfunction \((P=0.84)\). Across all subjects, a higher BNP was associated with a higher pulmonary artery systolic pressure \((\text{Spearman rho} 0.22, P<0.001)\).

Serum high sensitivity C-reactive protein (hsCRP) levels were available on all patients; there was a trend toward higher hsCRP levels among the HIV-infected individuals compared with uninfected controls \((2.5 \text{ mg/dL versus 2.2 mg/dL, } P=0.11)\). However, there was no association between higher hsCRP levels and diastolic dysfunction \((P=0.24)\) or was there any association between hsCRP levels and higher LV mass index \((P=0.53)\).

### Discussion

According to data from the Joint United Nations Program on HIV/AIDS, there are >33 million people living with HIV/AIDS worldwide\(^{19}\) and >1.1 million in the United States.\(^{20}\) Recently, the number of individuals aged 50 years and older living with HIV/AIDS has increased dramatically. In 2005, persons aged 50 and older accounted for 15% of new HIV/AIDS diagnoses and 29% of persons living with AIDS.\(^{21}\) As this population continues to age, chronic health conditions
such as cardiovascular disease will likely increase in importance. Higher rates of cardiovascular disease have already been reported in individuals with HIV infection along with higher rates of subclinical atherosclerosis. The widespread availability of combination antiretroviral therapy has resulted in dramatic reductions in the risk for AIDS-defining complications among HIV-infected patients. The impact of HIV infection (and its treatment) on cardiac function has not been well described, even though this is a common source of morbidity and mortality in aging HIV-uninfected patients. Here, we show that significant structural abnormalities such as decreased ejection fraction, valvular heart disease, and left ventricular hypertrophy are not more common in a well-characterized contemporary group of patients with HIV (most of who had been on long-term antiretroviral therapy) compared with uninfected controls. At the same time, we do demonstrate that HIV disease is independently associated with diastolic dysfunction, increased left atrial volumes, and increased LV mass index. All of these outcomes have been associated with higher mortality among uninfected patients. These observations support the growing concern that HIV infection may be linked with these diseases that have traditionally been associated with aging.

In our study, LV mass index was higher in HIV-infected individuals than the uninfected controls; this was true even after limiting our analysis to those without previous illicit drug use and to those without hypertension. The LV mass index, while elevated, did not exceed the gender-specific upper limit of normal in the majority of individuals and therefore did not imply clinical levels of left ventricular hypertrophy. Among our HIV-infected patients, a lower nadir CD4 count was associated with higher LV mass index. This finding was independent of risk factors that are traditionally associated with elevated LV mass including age, race, gender, diabetes mellitus, and hypertension. An association between LV mass index in HIV-infected women has been previously described, although this finding was no longer significant after adjusting for age. It is possible that HIV effect on LV mass may be secondary to subclinical atherosclerosis. We did not detect an association between previous coronary artery disease and LV mass index, although there were only 5% of patients with HIV with a history of CAD in our study. Our group has previously demonstrated an association between nadir CD4 count and subclinical atherosclerosis as assessed by carotid artery intima media thickness in individuals with HIV infection and other groups have found an association between CD4 and cardiovascular events. Of note, the nadir CD4+ T-cell count has been strongly associated with the level of immune activation; in turn, even among antiretroviral treated patients, the levels of immune activation remain elevated. The higher levels of inflammation present in patients with HIV may in theory contribute to increased LV mass, as has been suggested in studies of HIV-uninfected adults including individuals with systemic lupus erythematosus and rheumatoid arthritis.

The pathogenesis of HIV-associated diastolic dysfunction is likely multifactorial. First, although it remains controversial, several studies suggest that hypertension is associated with antiretroviral use, including prolonged duration of antiretroviral therapy and treatment with protease inhibitors. Hypertension was common in our HIV-infected study participants; however, this factor alone was unlikely to account for our findings as we still found an independent association between HIV infection and diastolic dysfunction both after adjustment for hypertension and after restricting the analysis to individuals without hypertension. Second, the increase in left ventricular mass index that we detected in our study may underlie the finding of mild diastolic dysfunction among patients with HIV. Third, it is possible that HIV or other associated viral infection may directly affect the myocardium. HIV-1 has been detected in endomyocardial biopsy specimens in patients with HIV with LV dysfunction, whereas other autopsy studies have detected sequences of HIV-1 in myocytes of patients with HIV at autopsy. Fourth, our group and others have shown that individuals with HIV infection have high rates of inflammation, which may predispose patients with HIV to diastolic dysfunction. In the uninfected population, higher levels of inflammatory markers such as hsCRP have been shown to be associated with diastolic dysfunction. Reversible and isolated diastolic dysfunction has been shown to occur in individuals with septic shock, a condition characterized by high levels of inflammation and in the setting of chronic inflammatory states such as rheumatoid arthritis. Fifth, in unadjusted analysis lower CD4 count and longer duration of NRTI use were associated with diastolic dysfunction, suggesting that advanced immunodeficiency and/or side effects from medication may mediate the development of this abnormality. NRTI use has previously been associated with cardiomyopathy and mitochondrial damage. Finally, subclinical atherosclerosis as assessed by carotid artery intima media thickness is common in HIV-infected individuals and therefore another possible mechanism underlying diastolic dysfunction may be underlying ischemic heart disease as well as increased arterial stiffness which has been reported in patients with HIV. In our study, diastolic dysfunction was not associated with a previous history of coronary artery disease but only 5% of HIV-infected individuals studied had this diagnosis.

The results of our study demonstrate that the echocardiographic findings associated with HIV infection during the early years of the epidemic have shifted. Left ventricular systolic dysfunction, right ventricular enlargement, and pericardial effusions were common findings before the widespread usage of antiretroviral medications. Previous studies demonstrated that pericardial effusions were associated with reduced survival and persistently low ejection fractions were associated with a high 1-year mortality rate. Our study suggests that LV and right ventricular systolic dysfunction and pericardial effusions are now rare, whereas mild diastolic dysfunction is common. The low rate of LV systolic dysfunction that we detected in our study may bode well for the aging population with HIV.

Our study was cross-sectional in nature and hence has several limitations commonly associated with this study design. Specifically, because our primary outcomes likely reflect a life-time of exposure to various risk factors, and because many of these factors are difficult to quantify retrospectively, a longitudinal study in which all such factors are measured is now needed. Still, we believe that our data are highly relevant, as they expand on those of earlier studies.
by using advanced techniques to assess diastolic dysfunction, by being carefully restricted and adjusted for potential confounders, and by including an uninfected control group.

The long-term clinical implications of our findings remain unclear. Among large population-based studies of asymptomatic middle-aged adults, diastolic dysfunction was strongly associated with both all-cause and cardiac mortality.\(^{47,48}\) Although unstudied at this time, it is likely that diastolic dysfunction will be predictive of mortality in the HIV population as well. Our findings suggest that caregivers should maintain a high clinical suspicion for cardiovascular disease, aggressively treat all traditional cardiovascular risk factors, and consider the possibility of diastolic dysfunction in HIV-infected individuals. However, in the absence of symptoms, we believe it is premature to recommend routine screening echocardiograms for HIV-infected adults.

It is also unclear as to whether the HIV-infected patients require any unique therapeutic interventions to manage or prevent cardiac dysfunction. Reduction of HIV-related inflammation using antiretroviral therapy would appear to be a reasonable approach, although the benefit of treatment on cardiac function remains unproven. Several studies including the Strategies for Management of Antiretroviral Therapy study and AIDS Clinical Trials Group 5142 suggest that using antiretroviral therapy prevents cardiovascular disease-associated outcomes (eg, myocardial infarction), at least in the short term.\(^{49,50}\) These studies were not able to specifically address the impact of antiretroviral treatment on cardiac function, but given the strong association between atherosclerotic disease and cardiac function, it is reasonable to assume that effective antiretroviral treatment will be beneficial. Longer term studies along with further investigations into the pathogenesis of HIV-associated cardiovascular disease will be essential in guiding standards of clinical care in the future.

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Disclosures

None.

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Hsue et al. HIV and Diastolic Function


CLINICAL PERSPECTIVE
With the advent of antiretroviral therapy, HIV-infected individuals are now faced with a new set of chronic health issues which include the development of cardiovascular disease. Previous echocardiographic studies of individuals with HIV demonstrated a high prevalence of reduced left ventricular systolic function and pericardial effusion; however, these studies were mostly performed before the widespread use of antiretroviral medication. In our study of contemporary HIV-infected individuals, we demonstrate that 50% have evidence of diastolic dysfunction which was independently associated with HIV infection after adjustment for traditional risk factors. HIV-infected individuals also had a higher left ventricular mass index which was associated with a low nadir CD4 cell count, suggesting that immunodeficiency may play a role in HIV-associated cardiovascular disease. Although diastolic dysfunction is predictive of mortality in individuals without HIV, the clinical implications of our findings remain unclear at this time and will require future prospective longitudinal studies. In addition, the therapeutic strategies to address diastolic dysfunction in the patient population with HIV are not known. Will control of HIV infection and HIV-related inflammation using antiretroviral therapy result in improvement in cardiac function and as a result clinical outcomes? Additional studies targeted at the mechanism of HIV-associated cardiovascular disease will be needed to answer this question and guide clinical care in the future.
Impact of HIV Infection on Diastolic Function and Left Ventricular Mass
Priscilla Y. Hsue, Peter W. Hunt, Jennifer E. Ho, Husam H. Farah, Amanda Schnell, Rebecca Hoh, Jeffrey N. Martin, Steven G. Deeks and Ann F. Bolger

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