Increased Coronary Vessel Wall Thickness in HIV-Infected Young Adults

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Background. Individuals with long-term human immunodeficiency virus (HIV) infection are at risk for premature vasculopathy and cardiovascular disease (CVD). We evaluated coronary vessel wall thickening, coronary plaque, and epicardial fat in patients infected with HIV early in life compared with healthy controls.

Methods. This is a prospective cross-sectional study of 35 young adults who acquired HIV in early life and 11 healthy controls, free of CVD. Time resolved phase-sensitive dual inversion recovery black-blood vessel magnetic resonance imaging (TRAPD) was used to measure proximal right coronary artery (RCA) wall thickness, and multidetector computed tomography (CT) angiography was used to quantify coronary plaque and epicardial fat.

Results. RCA vessel wall thickness was significantly increased in HIV-infected patients compared with sex- and race-matched controls (1.32 ± 0.21 mm vs 1.09 ± 0.14 mm, P = .002). No subject had discrete plaque on CT sufficient to cause luminal narrowing, and plaque was not related to RCA wall thickness. In multivariate regression analyses, smoking pack-years (P = .004) and HIV infection (P = .007) were independently associated with thicker RCA vessel walls. Epicardial fat did not differ between groups. Among the HIV-infected group, duration of antiretroviral therapy (ART) (P = .02), duration of stavudine exposure (P < .01), low-density lipoprotein cholesterol (P = .04), and smoking pack-years (P < .01) were positively correlated with RCA wall thickness.

Conclusions. This investigation provides evidence of subclinical coronary vascular disease among individuals infected with HIV in early life. Increased duration of ART, hyperlipidemia, and smoking contributed to proximal RCA thickening, independent of atherosclerotic plaque quantified by CT. These modifiable risk factors appear to influence early atherogenesis as measured by coronary wall thickness and may be important targets for CVD risk reduction.

Keywords. perinatal HIV; coronary artery; cardiovascular disease; antiretroviral therapy; smoking.

With access to effective combination antiretroviral therapy (ART), life expectancy of individuals with human immunodeficiency virus (HIV) is now approaching population norms [1]. Individuals who acquired HIV in early life represent the first generation of young adults growing up with lifelong exposure to HIV and ART. Long-term HIV and ART exposure are associated with elevated risks for non-AIDS-related complications, including metabolic abnormalities, and increased cardiovascular disease (CVD) risk [2].

The etiology of CVD risk in young adults with perinatal HIV infection is likely multifactorial. Chronic inflammation, aberrant immune activation, toxicity due to ART, and viral effects of HIV, in addition to traditional CVD risk factors, may contribute to increased CVD associated with HIV [3]. The relative impact of these risk factors on CVD in this population remains unknown.

The diagnosis of CVD typically occurs much later in life; thus, recent research has focused on the use of diagnostic imaging to evaluate subclinical alterations in cardiovascular structure and function in younger HIV-infected
populations. Although investigations have been performed using ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), these studies focused primarily on larger vessels that may not relate directly to the heart and coronary arteries. Studies that directly interrogated the coronary arteries utilized lumenography methods via multidetector coronary CT angiography (CCTA) in older patients with additional risk factors [4, 5]. To date, direct evaluation of the coronary vessel wall using the validated novel technique of phase-sensitive black-blood MRI [6, 7] has not been conducted in a younger HIV-infected population. Accurately imaging early indicators of coronary arterial disease, including vessel wall thickening and CT quantification of discrete coronary plaque, may shed insight into the effects of HIV and/or long-term ART exposure in young adults with lifelong HIV infection. This younger population is less affected by the cumulative consequences of traditional CVD risk on the coronary arteries.

The goal of this study was to assess early signs of coronary vascular disease in asymptomatic young adults with lifelong HIV infection compared with healthy controls using CT angiography and coronary vessel wall MRI. Further, we evaluated whether HIV-related factors and traditional CVD risk factors are associated with subclinical CVD in this cohort.

METHODS

Subjects
Adolescents and young adults who acquired HIV early in life (n = 35) and healthy controls (n = 11) were prospectively recruited for cross-sectional cardiovascular imaging and assessment of CVD risk. The study was completed between April 2010 and April 2013 at the National Institutes of Health Clinical Center (ClinicalTrials.gov identifiers: NCT00924365, NCT01656564). Subjects were excluded if they had known congenital or acquired CVD or contraindications to MRI. Controls were required to be healthy, ≥18 years old, without known significant medical conditions. There were no restrictions regarding antiretroviral use, CD4 count, or other comorbidities for HIV-infected participants. Written informed consent was obtained and the protocol was approved by the institutional review board of the National Institute of Allergy and Infectious Diseases. Participants completed a detailed history and physical including review of medical records to characterize CD4 nadir and lifetime ART exposure. Fasting laboratory tests included chemistry, lipid panel, CD4 count, HIV RNA load, and biomarkers of inflammation and immune activation (eg, percentage of CD4°CD38°DR+ cells and percentage of CD8°CD38°DR+ cells).

Coronary CT Angiography
Electrocardiography (ECG)–gated CCTA was performed and analyzed similarly to previously described techniques [4, 8–10]. When necessary, β-blockers were administered before imaging to lower heart rate. CCTA data were analyzed by the methods described previously. In brief, multiplanar reformatted coronary images were obtained using a 3-dimensional (3D) software tool (Virtual Place, AZE, Tokyo, Japan). Coronary plaque was defined as calcifications involving the coronary artery or non-calcified soft tissue density abutting the coronary lumen causing irregularity or luminal narrowing [11, 12]. Presence of coronary stenosis and number of plaques in each of the 17 American Heart Association segments was determined by 2 investigators in consensus who were blinded to subject clinical status.

Epicardial fat quantification was performed using a semiautomatic commercial software tool (Virtual Place) [13]. Epicardial fat was defined as the adipose tissue surrounding the heart between the myocardium and visceral pericardium.

Proximal Right Coronary Artery Wall MRI
Imaging of the proximal right coronary artery (RCA) during diastole was performed similar to that in published methodology [14]. Patient-specific time delay between the R-wave of the ECG and cardiac rest period was used for subsequent imaging. This was followed by a fast 3D ECG-gated free-breathing whole-heart scan for coronary localization [15].

Time-Resolved Coronary Wall Imaging
Single-slice free-breathing coronary vessel wall datasets were acquired using time-resolved acquisition of phase-sensitive dual inversion recovery (TRAPD) with a fixed inversion time (TI = 200 ms) and phase-sensitive reconstruction [6, 16]. Datasets were obtained in the proximal RCA segment, 1–3 cm distal to the vessel origin, at a location without noticeable stenosis or atherosclerotic disease on the coronary magnetic resonance angiography image and with guidance from the CCTA. Segmented k-space spiral acquisition (20 interleaves, acquisition window = 20 ms, α = 45°) was utilized with spectral spatial excitation for fat suppression [17], using a 32-channel phased-array cardiac coil and vectorcardiogram triggering [18]. Data from the anterior surface coil were used for image reconstruction. Repetition time was 1 cardiac cycle and spatial resolution was 0.69 × 0.69 × 8.0 mm.

Image Data Processing
Images were anonymized, blinding the processor to HIV status, and zoomed to 500%, and the center of the vessel wall was manually traced as an initial localization step. A 1-dimensional Gaussian-shape model was automatically fitted across the wall at all points along the wall’s center line. Outer and inner boundaries of the coronary wall were automatically identified as the 2 points of steepest gradients on the sides of each of the Gaussian shapes. Coronary artery wall thickness was measured as the average distance between identified inner and outer boundaries (Figure 1) [6].
Statistical Methods
Group comparisons were performed using nonparametric Wilcoxon rank-sum tests and $\chi^2$ tests where appropriate. Nonnormally-distributed variables such as triglyceride levels and HIV RNA load were log transformed to approximate a normal distribution. Univariate linear regression analyses were performed to evaluate associations between clinical variables and coronary vessel wall thickness. Variables identified as statistically significant on univariate analyses were included in multivariable regression analyses to identify independent predictors of coronary vessel wall thickness. Statistical significance was determined at a $P$ value of <.05. All statistical analyses were performed using SAS JMP software version 11.0 (SAS Institute, Cary, North Carolina).

RESULTS
We studied 35 young adults (age range, 15–29 years) who acquired HIV early in life and 11 HIV-uninfected controls (age range, 22–29 years) (Table 1). Thirty HIV-infected patients acquired HIV by vertical transmission and 5 patients contracted HIV postnatally through transfusion or feeding in infancy. Although 71% of the HIV-infected subjects were prescribed ART, only 43% had an HIV RNA level below detection limits.

There was no statistical difference in sex and race distributions between groups; however, HIV-infected subjects were significantly younger than controls. HIV-infected subjects had significantly greater blood pressure, but had significantly lower body mass index (BMI), total cholesterol, and high-density lipoprotein (HDL) cholesterol than controls. HIV-infected subjects were more likely to have ever smoked and had an increased number of pack-years, but these differences were not statistically significant.

No subject had atherosclerotic plaque causing significant luminal narrowing, and all identified coronary plaques were non-calcified. Coronary plaque on CT was present among 45% of controls, but only in 19% of HIV-infected subjects (Table 2). Epicardial fat volume did not differ between groups.

RCA vessel wall thickness in the HIV-infected group was $1.32 \pm 0.21$ mm compared with $1.09 \pm 0.14$ mm in the controls ($P = .002$). Smoking pack-years was significantly positively correlated with vessel wall thickness ($r = 0.44, P = .003$); however, this relationship was driven primarily by the correlation of smoking pack-years and RCA thickness within the HIV-infected population ($r = 0.44, P = .008$). Smoking pack-years and RCA thickness were not correlated in the control population ($r = 0.20, P = .6$). Although blood pressure, age, HDL cholesterol, and BMI differed between groups, none of these factors were correlated with RCA thickness. Moreover, there was no association between RCA thickness and levels of high-sensitivity C-reactive protein, D-dimer, pro-brain natriuretic peptide, homocysteine, insulin, or glucose for either group. In a subanalysis that excluded HIV-infected subjects not perinatally infected ($n = 5$), statistically significant differences in vessel wall thickness between the HIV-infected and control groups remained ($1.31 \pm 0.21$ mm vs $1.09 \pm 0.14$ mm, $P = .003$).
Epicardial fat volume was not correlated with either CT plaque associated with RCA thickness on MRI in either study population.

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Presence of coronary plaque on CT angiography was not associated with RCA thickness on MRI in either study population. Epicardial fat volume was not correlated with either CT plaque or proximal RCA thickness on MRI in either group. However, total and low-density lipoprotein (LDL) cholesterol levels were significantly higher in subjects with coronary plaque identified by CT (total cholesterol: 186 ± 31 vs 150 ± 27 mg/dL, P = .003; LDL cholesterol: 118 ± 43 vs 83 ± 23 mg/dL, P = .01).

In a multivariate regression analysis adjusting for age, sex, and BMI, HIV status was a significant predictor of RCA thickness (P = .007), as was smoking pack-years (P = .004) and LDL cholesterol (P = .02). To further correct for age differences between groups, a subanalysis excluding HIV-infected subjects aged <20 years was also performed, and the difference in proximal RCA thickness between groups remained significant (1.31 ± 0.21 mm vs 1.09 ± 0.14 mm, P = .002). A multivariate regression analysis adjusting for age, sex, BMI, LDL cholesterol, and smoking was also run in this subgroup analysis, and HIV (P = .009) again was a significant indicator of RCA thickness.

Among HIV-infected subjects, duration of ART, as well as duration of each class of ART, was positively correlated with vessel wall thickness (Table 3). Duration of stavudine use was the only individual agent significantly correlated with RCA thickness. ART and stavudine duration remained significantly correlated with RCA thickness.

Table 2. Coronary Artery Imaging and Epicardial Fat

<table>
<thead>
<tr>
<th>Imaging</th>
<th>HIV-Infected (n = 35)</th>
<th>Control (n = 11)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCA vessel wall thickness, mm</td>
<td>1.32 ± 0.21</td>
<td>1.09 ± 0.14</td>
<td>.002</td>
</tr>
<tr>
<td>RCA lumen, radius, mm</td>
<td>1.20 ± 0.42</td>
<td>1.03 ± 0.32</td>
<td>.2</td>
</tr>
<tr>
<td>RCA lumen, area, mm²</td>
<td>5.15 ± 3.30</td>
<td>3.64 ± 2.12</td>
<td>.14</td>
</tr>
<tr>
<td>CT angiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epicardial fat, mm³</td>
<td>27.5 ± 17.0</td>
<td>21.9 ± 3.0</td>
<td>.94</td>
</tr>
<tr>
<td>Average No. of coronary plaque lesions</td>
<td>0.32 ± 0.83</td>
<td>1.27 ± 2.24</td>
<td>.08</td>
</tr>
<tr>
<td>Individuals with coronary plaque, No. (%)</td>
<td>6 (19)</td>
<td>5 (45)</td>
<td>.1</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± standard deviation unless otherwise specified. Abbreviations: CT, computed tomography; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; RCA, right coronary artery.
Table 3. Correlation of Clinical Characteristics and Biomarkers With Coronary Vessel Wall Thickness Among HIV-Infected Subjects (n = 35)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Correlation Coefficient (r)</th>
<th>Model 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Model 2&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P Value</td>
<td>Estimate</td>
<td>P Value</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.10</td>
<td>0.6</td>
<td>-0.01</td>
</tr>
<tr>
<td>BMI, kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.09</td>
<td>0.6</td>
<td>0.003</td>
</tr>
<tr>
<td>Smoking pack-years, y</td>
<td>0.44</td>
<td>0.008</td>
<td>0.04</td>
</tr>
<tr>
<td>Duration of ART, y</td>
<td>0.38</td>
<td>0.02</td>
<td>0.014</td>
</tr>
<tr>
<td>Any ART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRTI</td>
<td>0.39</td>
<td>0.02</td>
<td>. . . .</td>
</tr>
<tr>
<td>NNRTI</td>
<td>0.34</td>
<td>0.046</td>
<td>. . . .</td>
</tr>
<tr>
<td>Protease inhibitor</td>
<td>0.39</td>
<td>0.02</td>
<td>. . . .</td>
</tr>
<tr>
<td>Stavudine</td>
<td>0.43</td>
<td>0.01</td>
<td>. . . .</td>
</tr>
<tr>
<td>Current CD4 count, cells/µL</td>
<td>0.35</td>
<td>0.04</td>
<td>. . . .</td>
</tr>
<tr>
<td>HIV load, log copies/mL</td>
<td>0.26</td>
<td>0.1</td>
<td>. . . .</td>
</tr>
<tr>
<td>hs-CRP, mg/mL</td>
<td>0.28</td>
<td>0.1</td>
<td>. . . .</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>0.39</td>
<td>0.02</td>
<td>. . . .</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>0.35</td>
<td>0.04</td>
<td>. . . .</td>
</tr>
<tr>
<td>Log triglycerides, mg/dL</td>
<td>0.36</td>
<td>0.04</td>
<td>. . . .</td>
</tr>
<tr>
<td>Epicardial fat, mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0.05</td>
<td>0.8</td>
<td>. . . .</td>
</tr>
<tr>
<td>Total No. of coronary plaque lesions</td>
<td>0.26</td>
<td>0.2</td>
<td>. . . .</td>
</tr>
<tr>
<td>Current CD4_CD38_DR %</td>
<td>0.24</td>
<td>0.2</td>
<td>. . . .</td>
</tr>
<tr>
<td>Current CD8_CD38_DR %</td>
<td>0.26</td>
<td>0.2</td>
<td>. . . .</td>
</tr>
</tbody>
</table>

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

<sup>a</sup> Model 1 is a multivariate fit model including age, BMI, years on ART, and smoking pack-years.

<sup>b</sup> Model 2 is a multivariate fit model including age, BMI, smoking pack-years, and years on stavudine.

Figure 2. Box plot of right coronary artery (RCA) vessel wall thickness of control subjects vs human immunodeficiency virus (HIV)-infected subjects with a viral load of <50 copies/mL and HIV-infected subjects with a viral load of >50 copies/mL. Bars represent full range of RCA vessel wall thickness within each group.
load <50 copies/mL had significantly thicker RCA walls than those with detectable viremia (Figure 2). ART duration was not correlated with either epicardial fat or presence of coronary plaque on CT angiography.

DISCUSSION

To our knowledge, this is the first study to evaluate the coronary arteries in a young HIV-infected population using both a coronary black-blood technique at high magnetic field (3T MRI) and lumenography method via CCTA. Together, these techniques demonstrate a significant increase in coronary vessel wall thickness on MRI without associated increases in coronary plaque or stenosis measured by CCTA in this young patient group compared with controls. Additionally, epicardial fat accumulation, a known predictor of CVD [13, 19], was not increased in this cohort. Within the HIV-infected group, smoking pack-years and length of ART, in particular stavudine, were independently associated with proximal RCA wall thickness.

Coronary vessel wall thickness measured by MRI in non-HIV-infected patients with subclinical coronary artery disease (CAD) found that vascular remodeling and, specifically, vessel wall thickening can precede formation of vulnerable coronary plaque [20]. Identification of early positive vascular remodeling at sites without noticeable stenosis therefore may be an even earlier predictor of CVD. Early identification of subclinical atherosclerosis and arterial wall thickening may also provide important insight into risk of developing end-organ vascular damage, including, but not limited to, HIV-associated myocardial damage, neurocognitive disorders, and/or renal damage.

Prior studies in HIV-infected subjects evaluated focal coronary artery atherosclerotic plaque [4, 5], usually including significantly older patients and/or imaging larger vessels [21–23]. In these studies, subjects were generally evaluated for gross luminal manifestations of CAD such as plaque burden or luminal narrowing. In comparison, our study targeted an early manifestation of CAD, namely, vascular wall thickening at sites without evidence of atheroma in younger patients. The proximal RCA was chosen as a representative vessel, and care was taken to target vessel locations without evidence of discrete plaque during imaging.

Smoking is a risk factor for CAD [24] and outward vascular remodeling [25]. Development of atherosclerosis due to smoking occurs via deposition of free radicals, resulting in increased oxidative stress [24]. Smoking was identified as an independent predictor of coronary vessel wall thickness in our cohort, as well. These data highlight the importance of addressing modifiable CVD risk factors such as smoking to optimize long-term health in the context of HIV infection.

Determining whether ART exposure or chronic inflammation associated with HIV are primary risk factors for vascular remodeling is challenging. Chronic inflammation and immune activation in HIV have been implicated in atherogenic and vascular remodeling processes [26–28]. Desvarieux et al showed increased carotid intima-media thickness (cIMT) in HIV-infected adults who never smoked [26]. Increased cIMT occurred most noticeably in those with longer duration of infection, irrespective of ART, indicating a potential role of chronic inflammation on vasculopathy. This and other cohort studies of cIMT in HIV-infected youth [3, 27] found increased proinflammatory factors associated with HIV, but failed to show a correlation between markers of inflammation and cIMT. Our cohort demonstrated similar results in the smaller coronary artery; although markers of immune activation were increased in the HIV-infected subjects, these factors were not related to vessel wall thickening. We cannot exclude the possibility that prior long-term exposure to inflammation led to accumulated vessel wall thickness that would not be detected in a cross-sectional assessment.

Evidence continues to accumulate implicating ART in development of CVD in HIV [3, 29–31]. Hyperlipidemia attributable to ART is one factor contributing to increased myocardial infarction in HIV [31]. Furthermore, adverse structural vascular changes in youth with early HIV infection are linked to ART exposure [3, 29, 32]. Our data support these observations; individuals exposed to ART for a longer duration had significantly thicker coronary vessel walls, and dyslipidemia was associated with increased RCA thickness. Sainz et al previously observed that HIV-infected children without viremia had significantly increased cIMT compared with controls [3]. Similarly, we found that RCA thickness was greatest in the subset of HIV-infected subjects without HIV viremia, which may act as a surrogate for ART adherence.

Mitochondrial toxicity as a result of nucleoside reverse transcriptase inhibitors (NRTIs), including stavudine, may be a mechanism of vascular remodeling in our population. Previous research has shown that metabolites of NRTIs may compete with binding sites of the mitochondrial electron transport chain, thus causing increases in mitochondrial reactive oxygen species (ROS) [33, 34]. Modulation of ROS in the vasculature has been associated with vasculopathy and atherosclerosis [35], and may be an initiating event in subclinical vasculopathy in this cohort.

The sample size of the current study was relatively small and may limit the generalizability of our findings to the larger population of individuals infected with HIV in early life surviving into adulthood. Furthermore, the cross-sectional study design prevents us from determining causality, especially with respect to ART exposure and its effects on vessel wall thickening. Although not statistically different, there was a higher proportion of women in the control group, and it is possible that sex differences in vessel wall thickness exist. However, sex was included in multivariable analyses in which the differences in vessel wall
thickness between HIV and control groups persisted. Our HIV-infected and control groups were not age-matched. The effect of younger age in the HIV cohort, if anything, should have predisposed the vessel wall thickness to be less than that of controls. Indeed, the higher prevalence of noncalcified coronary plaque within the control group may be related to their relatively older age. Furthermore, we included age in multivariate analyses and we performed subanalyses excluding HIV-infected patients aged <20 years. The effect of HIV status on vessel wall thickness persisted in these analyses. Future investigations in HIV-infected youth with larger cohort sizes are needed to verify these observations.

Another limitation is the 8-mm slice thickness used in imaging the coronary vessel wall. This was necessary to maintain the temporal resolution of this method to suppress cardiac motion while obtaining a robust fat suppression necessary to delineate the vessel wall from the surrounding fat. Phase-sensitive coronary wall imaging and TRAPD techniques with the current applied slice thickness have been previously validated and were able to differentiate vessel wall thickness in patients with risk factors and known CAD from healthy controls [6, 7].

In summary, our study is the first to demonstrate increased coronary vessel wall thickness, a measure of premature vasculopathy, in young adults with HIV infection from early life. Duration of ART, dyslipidemia, and smoking were associated with accelerated coronary arterial remodeling in this population. This study also demonstrates that a magnetic resonance technique for measuring vessel wall thickness is a useful non-invasive method to assess subclinical vasculopathy and may have application as a biomarker for early vascular disease in HIV-infected patients. Further investigation regarding pathogenesis of ART-mediated vessel wall thickening may be integral both for prevention and treatment of non-AIDS-related complications.

Notes

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Potential conflicts of interest. All authors: No potential conflicts of interest.

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