Radiology: Cardiothoracic Imaging

ORIGINAL RESEARCH

Association of Coronary Wall Thickening and Diminished Diastolic Function in Asymptomatic, Low Cardiovascular Disease–Risk Persons Living with HIV

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Conflicts of interest are listed at the end of this article.

See also commentary by Luetkens and Bischoff in this issue.

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Purpose: To assess early subclinical coronary artery disease (CAD) burden and its relation to myocardial function in asymptomatic persons living with HIV (PLWH) who are at low risk for cardiovascular disease (CVD).

Materials and Methods: In this prospective, HIPAA-compliant study (ClinicalTrials.gov NCT01656564 and NCT01399385) conducted from April 2010 to May 2013, 74 adult PLWH without known CVD and 25 matched healthy controls underwent coronary MRI to measure coronary vessel wall thickness (VWT) and echocardiography to assess left ventricular function. Univariable and multivariable linear regression analyses were used to evaluate statistical associations.

Results: For PLWH, the mean age was 49 years ± 11 (SD), and the median Framingham risk score was 3.2 (IQR, 0.5–6.6); for matched healthy controls, the mean age was 46 years ± 8 and Framingham risk score was 2.3 (IQR, 0.6–6.1). PLWH demonstrated significantly greater coronary artery VWT than did controls (1.47 mm ± 0.22 vs 1.34 mm ± 0.18; $P = .006$) and a higher left ventricular mass index (LVMI) (77 ± 16 vs 70 ± 13; $P = .04$). Compared with controls, PLWH showed altered association between coronary artery VWT and both E/A (ratio of left ventricular–filling peak blood flow velocity in early diastole [E wave] to that in late diastole [A wave]) ($P = .03$) and LVMI ($P = .04$). In the PLWH subgroup analysis, coronary artery VWT increase was associated with lower E/A ($P < .001$) and higher LVMI ($P = .03$), indicating restricted diastolic function. In addition, didanosine exposure was associated with increased coronary artery VWT and decreased E/A ratio.

Conclusion: Asymptomatic low-CVD-risk PLWH demonstrated increased coronary artery VWT in association with impaired diastolic function, which may be amenable to follow-up studies of coronary pathogenesis to identify potential effects on the myocardium and risk modification strategies.

Clinical trial registration nos. NCT01656564 and NCT01399385

Supplemental material is available for this article.

As effective antiretroviral therapy (ART) increases the life expectancy for persons living with HIV (PLWH), non–AIDS-related health concerns are increasingly common. Growing evidence suggests that the burden of cardiovascular disease (CVD) is higher in these individuals than in those without HIV (1), with an estimated fourfold higher rate of sudden cardiac death among PLWH compared with the general population (2). Nevertheless, the precise pathophysiologic mechanism underscoring this enhanced mortality rate is unclear. Consequently, early identification of subclinical CVD in young PLWH is an urgent necessity and could potentially open avenues for more effective intervention and disease management.

Coronary artery calcium, measured with cardiac CT, is a strong marker of subclinical atherosclerosis and predicts future CVD events in the general population. However, coronary artery calcium may be less valuable in PLWH, in whom noncalcified coronary plaque predominates (3–7). Coronary CT angiography is used to detect and characterize noncalcified coronary plaque (6). However, coronary CT angiography might not be suitable for long-term follow-up studies, particularly in young PLWH and broader demographic groups that include women.

Despite a preserved global myocardial function, early diastolic dysfunction and myocardial strain abnormalities have been documented in PLWH (8,9). For example, Hsue et al (9) found that middle-aged PLWH (median age, 47 years) were more than twice as likely to have diastolic dysfunction as controls without HIV. In that study, PLWH had lower E/A (ratio of left ventricular [LV]–filling peak blood flow velocity in early diastole [the E wave] to that in late diastole [the A wave]), higher LV masses, and higher

Abbreviations

ART = antiretroviral therapy, ASE = American Society of Echocardiography, AUC = area under the receiver operating characteristic curve, CAD = coronary artery disease, CVD = cardiovascular disease, E/A = ratio of LV-filling peak blood flow velocity in early diastole (the E wave) to that in late diastole (the A wave), E/e′ = ratio of early diastolic left ventricular inflow velocity to septal or lateral mitral annular velocity, FRS = Framingham risk score, LV = left ventricle, LVMI = LV mass index, PLWH = persons living with HIV, RCA = right coronary artery, TRAPD = time-resolved acquisition of phase-sensitive dual inversion-recovery, VWT = vessel wall thickness

Summary

Increased coronary artery vessel wall thickness in asymptomatic middle-aged persons living with HIV was significantly associated with impaired diastolic function.

Key Points

- Middle-aged asymptomatic persons living with HIV at low risk for cardiovascular disease showed increased subclinical coronary atherosclerosis manifested as increased coronary artery vessel wall thickness at MRI (1.47 mm ± 0.22 vs 1.34 mm ± 0.18; $P = .006$).
- The increased subclinical coronary artery disease was associated with increased restriction of diastolic function indicated with lower ratio of left ventricular–filling peak blood flow velocity in early diastole to that in late diastole ($P < .001$) and higher left ventricular mass index ($P = .03$).

Keywords

Coronary Vessel Wall Thickness, Diastolic Function, HIV, MRI, Echocardiography, Atherosclerosis

left atrium indexes, all of which were associated with higher cardiovascular mortality in individuals without HIV. Although coronary artery disease (CAD) is traditionally linked with aging, coronary artery pathology develops early in PLWH (10). In a study of adolescents and young adults (mean age, 22 years ± 4 [SD]) who acquired HIV early in life, increased coronary vessel wall thickening (coronary artery VWT) was identified and may have represented early CAD (10). Therefore, it is important to leverage the detailed information provided by coronary vessel wall MRI to elucidate the early cardiovascular pathogenesis, mechanisms, and complications associated with HIV in a middle-aged, yet relatively young, PLWH group that was previously studied with coronary CT angiography.

The current study aimed to assess the difference in CAD burden using MRI in a sample of adult PLWH with low Framingham score (FRS) and no CVD history compared with matched healthy controls. The second objective of the study was to determine whether subclinical CAD in PLWH is associated with echocardiographic measures of myocardial function.

Materials and Methods

Participants

We prospectively evaluated 74 adult PLWH and 25 age-, sex-, and race-matched controls from April 2010 to May 2013 at the National Institutes of Health (ClinicalTrials.gov NCT01656564 and NCT01399385). Written informed consent was obtained from each participant. The protocol was approved by the institutional review board of the National Institutes of Health and was Health Insurance Portability and Accountability Act compliant.

Individuals were recruited through self-referral and in response to local advertisements (Fig 1). Participants were excluded if they had a contraindication to MRI or known CVD, including previous myocardial infarction, coronary revascularization, coronary bypass, angina, heart failure, or stroke. There were no restrictions regarding ART use, HIV suppression, or $CD4^+$ T-cell count. Controls were documented as negative for HIV and were required to be healthy, with no known significant medical conditions, including CVD. Targeted recruitment of controls was performed to match the corresponding age (±5 years), sex, and racial distribution of the PLWH group at a ratio of approximately 3:1 (PLWH cases to controls). A detailed medical history, physical examination, and laboratory tests were obtained for each participant, including review of ART exposures and traditional CVD risk factors. Each participant had laboratory determinations that included the following: a fasting lipid panel, $CD4^+$ and $CD8^+$ T-cell count, and HIV viral load.

Eighty-seven of the 99 participants who completed this study were previously recruited and included in a separate study (11) that was designed to evaluate diffuse myocardial steatosis and fibrosis and its relationship to myocardial function, whereas the current report represents the findings of coronary VWT in association with increased restriction of diastolic function. Because of the requirement of contrast enhancement in the previous study, the examinations for this report were performed at different times with separate MRI sessions using different MRI techniques and equipment (different vendor), and these data have not been presented elsewhere.

Imaging Protocols

Transthoracic echocardiography.— Transthoracic echocardiography was performed using a Philips IE33 system and analyzed using Prosolv Cardiovascular, version 4.0 (Fujifilm). Standard views were obtained with participants in the left lateral recumbent position. Cardiac measurements were performed according to the American Society of Echocardiography (ASE) guidelines (12). Mitral inflow velocity was measured by placing a pulse-wave Doppler probe in the mitral valve area to record the speed at which blood flows from the left atrium to the LV during diastole. Recordings were obtained with the pulsed Doppler sample volume at the level of the mitral leaflet tips during maximal opening in diastole. Tissue Doppler recordings were measured with sample volumes at both the septal mitral annulus and lateral mitral annulus. The E/A was calculated using the early diastolic peak LV blood inflow velocity (E wave) to late peak LV blood inflow velocity (A wave).

The ratio of early diastolic LV inflow velocity to septal or lateral mitral annular velocity (LV E/e′) was calculated. Other measurements related to diastolic function included septal e′ velocity (or lateral e′), E/e′ ratio left atrial volume index, LV mass index (LVMI), and tricuspid regurgitation. LV diastolic dysfunction was identified using the 2016 ASE recommendations

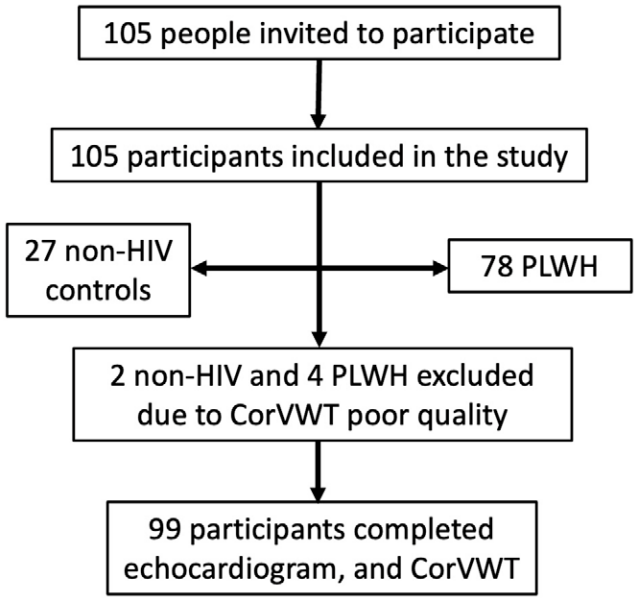

Figure 1: Flow diagram shows initial number of participants, final numbers, and reasons for exclusion. CorVWT = coronary vessel wall thickness, PLWH = persons living with HIV.

(13): mild LV diastolic dysfunction (abnormal relaxation, E/A ≤ 0.8), moderate to severe LV diastolic dysfunction (pseudonormal pattern, 0.8 ≤ E/A < 2), and a restrictive pattern (E/A ≥ 2). Additional parameters for diastolic dysfunction included the following: septal e′ velocity less than 7 cm/sec or lateral e′ velocity less than 10 cm/sec, mean E/e′ greater than 14, left atrial volume index greater than 34 mL/m^2, peak tricuspid regurgitation velocity greater than 2.8 m/sec, and LVMI greater than 95 g/m^2 for female participants and greater than 115 g/m^2 for male participants. The complete algorithm for diastolic function assessment using these criteria is described in detail by Nagueh et al in the ASE guidelines (13). Echocardiographic measurements were performed (H.H., with 20 years of experience in echocardiography).

Coronary VWT at MRI.— Coronary VWT MRI was performed at 3 T (Philips Achieva). This method has previously demonstrated an intraobserver, interobserver, and interexamination agreement for coronary VWT measurement of 0.98 mm, 0.97 mm, and 0.92 mm, respectively (14). Imaging of the coronary artery was performed during diastole according to published validated methods (10,14,15).

To localize the right coronary artery (RCA), fast coronary MR angiography was performed for the RCA without intravenous contrast material by using adiabatic T2-prepared pulse sequence (10,14,15). Briefly, navigator-gated three-dimensional segmented k-space gradient-echo coronary MR angiography was performed using repetition time of 8 msec, echo time of 2.1 msec, α of 20 degrees, field of view of 270 mm × 270 mm, and in-plane resolution of 0.7 × 0.7 mm^2. Single-section free-breathing multiple burst mode coronary vessel wall time frames were acquired during diastasis by using time-resolved acquisition of phase-sensitive dual inversion-recovery (TRAPD) with a fixed base inversion time (200 msec) and phase-sensitive reconstruction (10,14,15). The time frame with the highest-quality visualization of the coronary wall was chosen for measurement of coronary artery VWT.

Coronary artery VWT images were obtained for the proximal RCA segment, 1–3 cm distal to the vessel origin, at a location without noticeable stenosis (Fig 2). Image quality assessment and coronary artery VWT analysis were performed offline using an in-house custom-built software tool developed using MATLAB software, version 7.8 (MathWorks) (10,14,15). Briefly, to initialize the localization process, images were zoomed to 500%, and a manual delineation of the vessel wall's center was performed. Subsequently, an automated fit was carried out using a unidimensional Gaussian-shaped model along all points of the designated centerline. The outer and inner boundaries of the coronary wall were automatically detected as the two points exhibiting the steepest gradients on each side of the Gaussian shape model. Coronary arterial wall thickness was then computed as the mean distance between the aforementioned inner and outer boundaries. Analysis was performed by K.Z.A.E. (with >15 years of experience in cardiovascular imaging and image analysis), who was blinded to the HIV status of the participants at the time of performing the measurements.

Statistical Analysis

Demographic characteristics are reported as means ± SDs for continuous normal data, medians (IQRs) for continuous nonnormally distributed data, and frequencies (percentages) for categorical data. Based on previous reports of coronary artery VWT in PLWH (10), a total sample size of 56 (28 per group) would provide 80% power to detect a 0.15-mm difference in coronary artery VWT with an estimated population mean for coronary artery VWT of 1.32 mm and an SD of 0.20 mm. Additional participants were recruited within the PLWH group to increase the likelihood of detecting associations between HIV-specific characteristics and coronary artery VWT. HIV status was assessed as a dichotomous variable: "yes" for PLWH or "no" for controls.

The initial phase of the analysis included evaluating the increase in coronary wall thickness in the PLWH cohort relative to that of their matched HIV-negative counterparts, affirming the findings previously documented in the literature (10,16). Univariable and multivariable linear regression analyses were performed to study the association between coronary artery VWT as the outcome variable, and age, smoking history in packs per year, FRS, diabetes status, and HIV status as potential independent predictors. The multivariable regression rule of 10 events per explanatory variable was used to determine the number of potential surrogate variables included in the primary regression analysis (17). Statistically significant predictors ($P < .05$) in the univariable regression were consequently included in the multivariable regression analyses. Stepwise regression models were calculated using a P value threshold of .25 to enter and .1 to leave.

The central phase of the analysis was anchored on the interplay between diastolic dysfunction in HIV, indicated by E/A and LVMI, and its association with coronary artery VWT. Similar to the aforementioned coronary artery VWT analyses, regression analyses were performed to investigate the association between diastolic function measured by E/A and LVMI

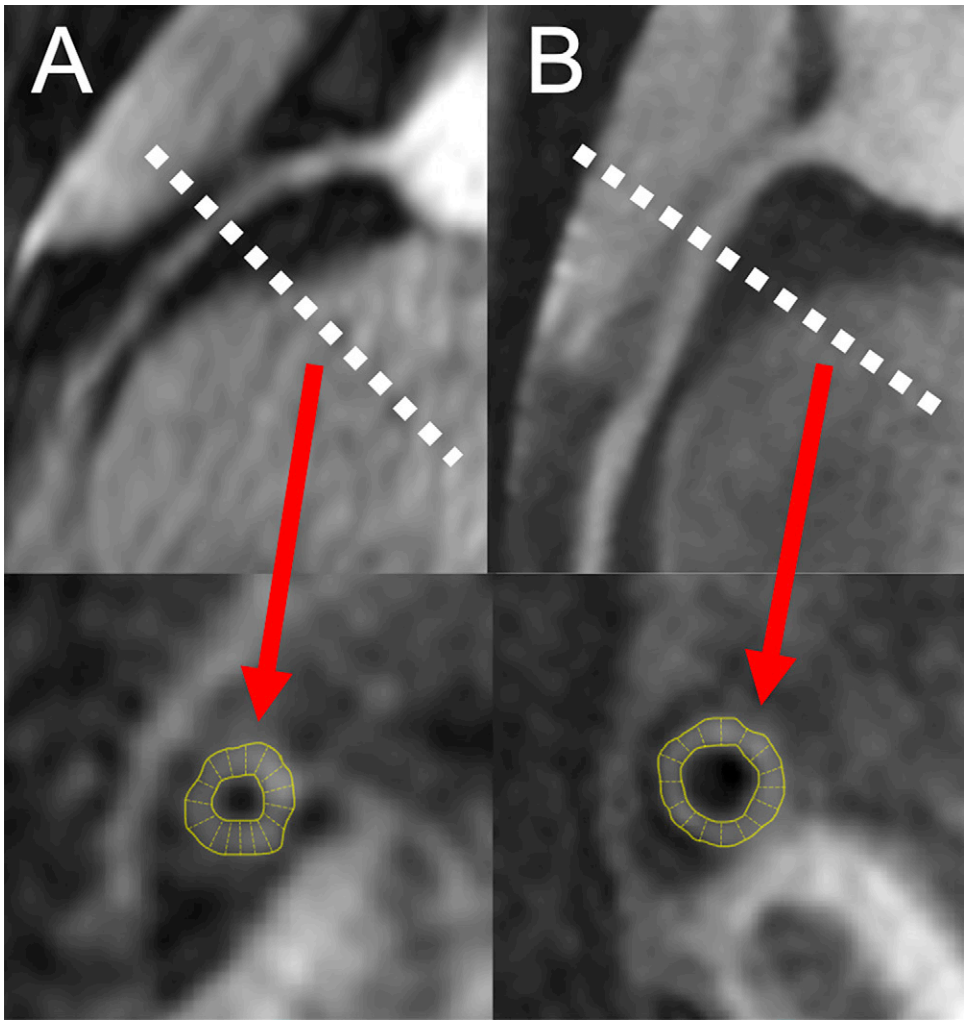

Figure 2: MR angiograms (top row) of the right coronary arteries in two persons living with HIV (PLWH) show location of cross-section (dotted lines) of coronary vessel wall image (bottom row) and the corresponding automatic wall thickness measurement. **(A)** Image from 50-year-old male PLWH with increased coronary vessel wall thickness of 1.5 mm and grade 1 diastolic dysfunction. **(B)** Image from 52-year-old male PLWH with coronary vessel wall thickness of 1.2 mm and normal diastolic function.

as the outcome variables and age, smoking history in packs per year, FRS, diabetes status, coronary artery VWT, HIV status, and the potential interaction between coronary artery VWT and HIV status.

Subsequently upon the finding of HIV status being a significant predictor or an interaction variable, further subgroup analyses were conducted in the PLWH group, considering and adjusting for the effect of HIV-specific characteristics. Years of HIV infection, total duration of ART, and duration of individual ART agents with at least 10 participants reporting exposure were assessed for potential relationships with coronary artery VWT, E/A, and LVMI.

For thoroughness, we conducted a secondary analysis involving the control group, reinforcing the findings from aforementioned all-cohort examination.

Last, logistic regression and receiver operating characteristic analyses were performed to determine odds ratios, the area under the receiver operating characteristic curve (AUC), and the cutoff values (using the Youden index method) for the independent variables significantly associated with impaired diastolic function.

P values less than .05 were considered to indicate statistically significant differences. Statistical analyses were performed using R software, version 4.2.2 (R Foundation for Statistical Computing).

Results

Participant Characteristics

Demographic and clinical characteristics of the 74 PLWH (mean age, 49 years ± 11 [SD]; 55 male and 19 female) and 25 control (mean age, 46 years ± 8; 19 male and six female) study participants are presented in Table 1. PLWH and controls were similar with regard to blood pressure and FRS; however, PLWH had significantly lower low-density lipoprotein cholesterol levels and more smoking exposure, whereas controls had a higher body mass index (calculated as weight in kilograms divided by height in meters squared). PLWH had a significantly greater coronary

Table 1: Demographic and Clinical Characteristics of Study Participants

Variable	PLWH (n = 74)	Controls (n = 25)	P Value
Age (y)	49 ± 11	46 ± 8	.20
Male/female participants	55/19	19/6	.90
Race/ethnicity			.50
Black	41 (55.4)	15 (60.0)	
White	22 (29.7)	6 (24.0)	
Other	11 (15.0)*	4 (16.0)†	
Framingham risk score‡	3.2 (0.5–6.6)	2.3 (0.6–6.1)	.54
Body mass index	27 ± 4	29 ± 4	.01
Systolic blood pressure (mm Hg)	124 ± 12	122 ± 13	.49
Diastolic blood pressure (mm Hg)	78 ± 9	75 ± 10	.22
HDL cholesterol level (mg/dL)§	46 ± 13	45 ± 13	.8
LDL cholesterol level (mg/dL)§	96 ± 28	114 ± 35	.02
Triglyceride level (mg/dL)	138 ± 88	126 ± 72	.51
$CD4^+$ T cells (cells/mm^3)‖	593 ± 272	884 ± 359	<.001
$CD4^+/CD8^+$ T-cell ratio	0.88 ± 0.62	2.13 ± 0.84	<.001
Medical history			
Current lipid-lowering therapy	27 (36)	4 (16)	.046
Hypertension	23 (31)	5 (20)	.28
Diabetes	8 (11)	0 (0.0)	.02
History of smoking	49 (66)	9 (36)	.008
Smoking history (packs per year)‡	2 (0–15)	0 (0–1.5)	.002
$CD4^+$ nadir < 200 cells/mm^3	27/66 (41)	...	...
Duration of HIV infection (y)	13.6 ± 7.6	...	...
Duration of ART exposure (y)	8.4 ± 5.9	...	...
HIV viral RNA load < 40 copies/mL	65 (88)	...	...

Note.—Unless otherwise specified, data are means ± SDs or numbers with percentages in parentheses. Body mass index calculated as weight in kilograms divided by height in meters squared. ART = antiretroviral therapy, HDL = high-density lipoprotein, LDL = low-density lipoprotein, PLWH = persons living with HIV.
* Eight persons of Hispanic ethnicity and three of mixed ethnicity.
† Three persons of Hispanic ethnicity and one of mixed ethnicity.
‡ Data are medians, with IQRs in parentheses.
§ To convert values to mmol/L, multiply by 0.0259.
‖ To convert values to $\times 10^9$/L, multiply by 0.001.

artery VWT (1.47 mm ± 0.22) than controls (1.34 mm ± 0.18; P < .001) (Table 2, Fig 3). Although we found no evidence of a difference between groups in echocardiography-measured ejection fraction and E/A, as well as tissue Doppler ratios, PLWH had greater LV mass indexed to body surface area (77 ± 16 vs 70 ± 13; P = .04). Indeterminate (five of 74 [6.8%] vs 0 of 25 [0%]) or definite (five of 74 [6.8%] vs 0 of 25 [0%]) diastolic dysfunction was more frequent in PLWH compared with control participants; however, the difference between the two groups was not statistically significant (P = .061).

Association of Coronary Wall Thickness with HIV

In addition to the difference observed in coronary artery VWT by HIV status, age, smoking history in packs per year, FRS, and diabetes were independently associated with coronary artery VWT in the univariable regression analyses (Table 3). In the multivariable regression, age and HIV status remained the only variables significantly associated with coronary artery VWT (Table 3). Figure 4A demonstrates this multivariable regression association between coronary artery VWT and age, with wall thickening further accentuated by HIV infection and the presence of diabetes.

Among PLWH (Table 4), coronary artery VWT was not associated with the years of HIV infection or the duration of total ART exposure. However, duration of didanosine was associated with increased coronary artery VWT (β = 0.032; P < .001). Separately associated with coronary artery VWT were age (β = 0.005; P = .04), diabetes (β = 0.177; P = .03), and smoking pack-years (β = 0.002; P = .03). Multivariable stepwise regression of coronary artery VWT among PLWH found that smoking history in packs per year (β = 0.002; P = .02) and duration of didanosine exposure (β = 0.033; P < .001) were the only variables jointly associated with increased coronary artery VWT.

Table 2: Coronary Artery Imaging and Echocardiographic Measurements

Variable	PLWH (n = 74)	Controls (n = 25)	P Value
Coronary artery vessel wall thickness (mm)	1.47 ± 0.22	1.34 ± 0.18	.006
Echocardiographic measurements			
LV mass index (g/m²)	77 ± 16	70 ± 13	.04
LV ejection fraction (%)	61 ± 6	63 ± 4	.06
LA volume index (g/m²)	26 ± 10	26 ± 6	.68
Septal e′ (cm/sec)	9.1 ± 2.5	9.9 ± 2.6	.18
Lateral e′ (cm/sec)	13.0 ± 3.0	14.1 ± 3.3	.21
E/A ratio	1.41 ± 0.46	1.54 ± 0.51	.25
E/e′ ratio	7.95 ± 2.24	7.74 ± 2.84	.76
TR velocity (m/sec)	2.24 ± 0.26	2.29 ± 0.21	.45
Diastolic dysfunction			.061
None	64 (86.4)	25 (100)	
Indeterminate	5 (6.8)	0 (0)	
Definite	5 (6.8)	0 (0)	

Note.—Unless otherwise specified, data are means ± SDs or numbers with percentages in parentheses. A = late diastolic transmitral flow velocity, e′ = early diastolic mitral annular tissue velocity, E = early diastolic transmitral flow velocity, LA = left atrium, LV = left ventricle, PLWH = persons living with HIV, TR = tricuspid regurgitation.

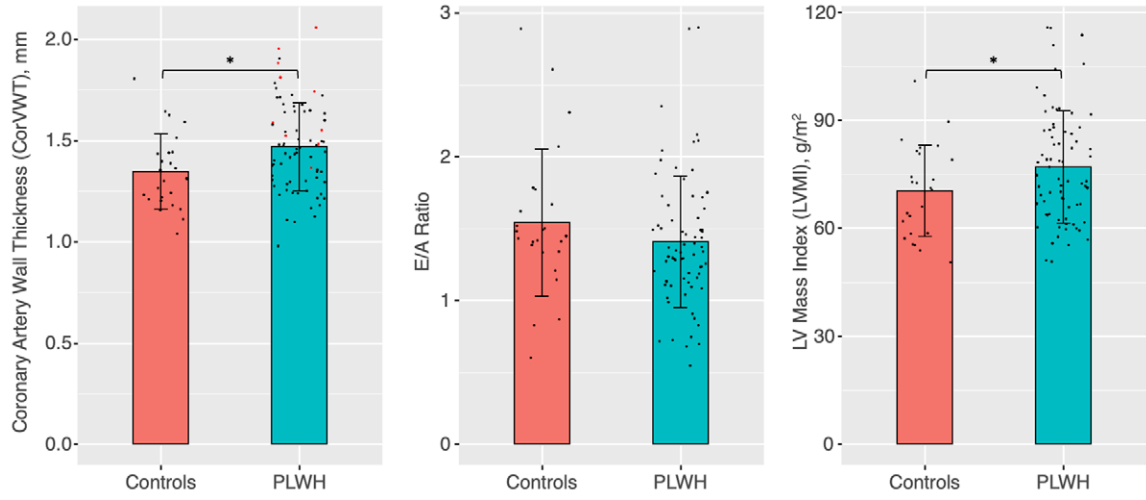

Figure 3: Scatterplots, means, and SDs of coronary artery vessel wall thickness (CorVWT), E/A (ratio of left ventricular–filling peak blood flow velocity in early diastole [the E wave] to that in late diastole [the A wave]), and left ventricular mass index (LVMI) in persons living with HIV (PLWH) and the control groups. Red dots in the leftmost plot indicate PLWH with diastolic dysfunction. * $P < .05$.

Association of Diastolic Dysfunction with Coronary VWT in PLWH

The all-cohort E/A univariable analysis (Table 3) showed no significant association between smoking history in packs per year and E/A, which did not differ by HIV status. In multivariable analysis, only age and the interaction between coronary artery VWT and HIV status remained associated with E/A ratio.

In a subanalysis limited to PLWH, neither smoking, CD4⁺/CD8⁺ counts, or years of HIV infection were associated with E/A. Variables that were identified and remained significantly associated with E/A in the multivariable regression model included coronary artery VWT (β = -0.484; P = .04), age (β = -0.017; P < .001), and duration of didanosine exposure (β = -0.037; P = .05) (Table 4).

In the all-cohort LVMI univariable analysis, age, FRS, diabetes, coronary artery VWT, and coronary artery VWT interaction with HIV status were all independent factors associated with LVMI. In the multivariable regression, FRS (β = 0.687; P = .03) and coronary artery VWT interaction with HIV status (β = 14.098; P = .04) remained, jointly, the only factors significantly associated with LVMI (Table 3, Fig 4C). In the PLWH group regression analysis for LVMI (Table 4), variables that remained

Table 3: Univariable and Multivariable Linear Regression in the Entire Cohort between Candidate Independent Predictors with Coronary Vessel Wall Thickness, E/A, and Left Ventricular Wall Thickness

	Univariable		Multivariable	
Variable	Coefficient β (SE)	*P* Value	Coefficient β (SE)	*P* Value
Coronary artery VWT (entire cohort)				
Age in years	0.006 (0.002)	.004	0.005 (0.002)	.03
Smoking history in packs per year	0.003 (0.001)	.004	...	...
FRS	0.009 (0.005)	.049	...	...
Diabetes (yes)	0.206 (0.078)	.01	0.130 (0.079)	.10
HIV status (yes)	0.128 (0.049)	.01	0.101 (0.048)	.04
E/A (entire cohort)				
Age in years	-0.021 (0.004)	<.001	-0.018 (0.004)	<.001
Smoking history in packs per year	-0.003 (0.002)	.17	...	...
FRS	-0.029 (0.009)	.003	...	...
Diabetes (yes)	-0.461 (0.168)	.007	...	...
Coronary artery VWT in mm	-0.709 (0.211)	.001	...	...
HIV status (yes)	-0.134 (0.109)	.22	...	...
Coronary VWT HIV status*				
Controls	-0.635 (0.243)	.01	...	...
PLWH	-0.684 (0.216)	.002	-0.470 (0.206)	.03
LVMI (entire cohort)				
Age in years	0.333 (0.149)	.03	...	...
Smoking history in packs per year	0.053 (0.07)	.45	...	...
FRS	0.859 (0.311)	.01	0.687 (0.311)	.03
Diabetes (yes)	11.279 (5.497)	.04	...	...
Coronary artery VWT in mm	18.575 (6.776)	.01	...	...
HIV status (yes)	6.607 (3.458)	.06	...	...
Coronary artery VWT HIV status*				
Controls	13.394 (7.76)	.09	...	...
PLWH	16.823 (6.871)	.02	14.098 (6.848)	.04

Note.—E/A = ratio of left ventricular–filling peak blood flow velocity in early diastole (the E wave) to that in late diastole (the A wave), FRS = Framingham risk score, LVMI = left ventricular mass index, PLWH = persons living with HIV, SE = standard error, VWT = vessel wall thickness.
* Interaction between coronary VWT and HIV.

significantly associated with LVMI included coronary artery VWT (β = 18.271; *P* = .03) and FRS (β = 1.013; *P* = .004).

Finally, age and coronary artery VWT remained as significant variables associated with impaired diastolic function, with a joint AUC of 0.84 (95% CI: 0.73, 0.94; *P* < .001), and an AUC for coronary artery VWT alone of 0.77 (95% CI: 0.65, 0.90; *P* = .001). The cutoff value of coronary artery VWT was 1.47 mm (odds ratio, 1.59; 95% CI: 1.11, 2.28). In the healthy control group analysis, none of the previously considered independent variables were associated with E/A or LVMI (Table S1).

Discussion

In this study, we found that PLWH with low FRS and without known CVD had increased coronary VWT and LVMI compared with healthy controls. This association with HIV remained significant, independently of age, and was accentuated by the presence of diabetes in PLWH. The increased coronary artery VWT was independently associated with elevated LVMI, reduction of E/A, and impaired diastolic function. Among PLWH, coronary artery VWT was also related to the duration of didanosine exposure and negatively associated with a decreased diastolic function (decreased E/A).

A considerable body of literature pertains to the variation in coronary plaque composition and volume among PLWH compared with persons who are HIV negative. In a recent meta-analysis, Soares et al (18) deduced that PLWH are more likely to have a higher prevalence of noncalcified and mixed coronary plaques, as well as high-risk plaque characteristics, including positive remodeling and low-attenuation plaque, in contrast to HIV-negative individuals. Another comprehensive review of cardiovascular imaging studies showed that HIV infection is associated with an escalated risk of cardiovascular

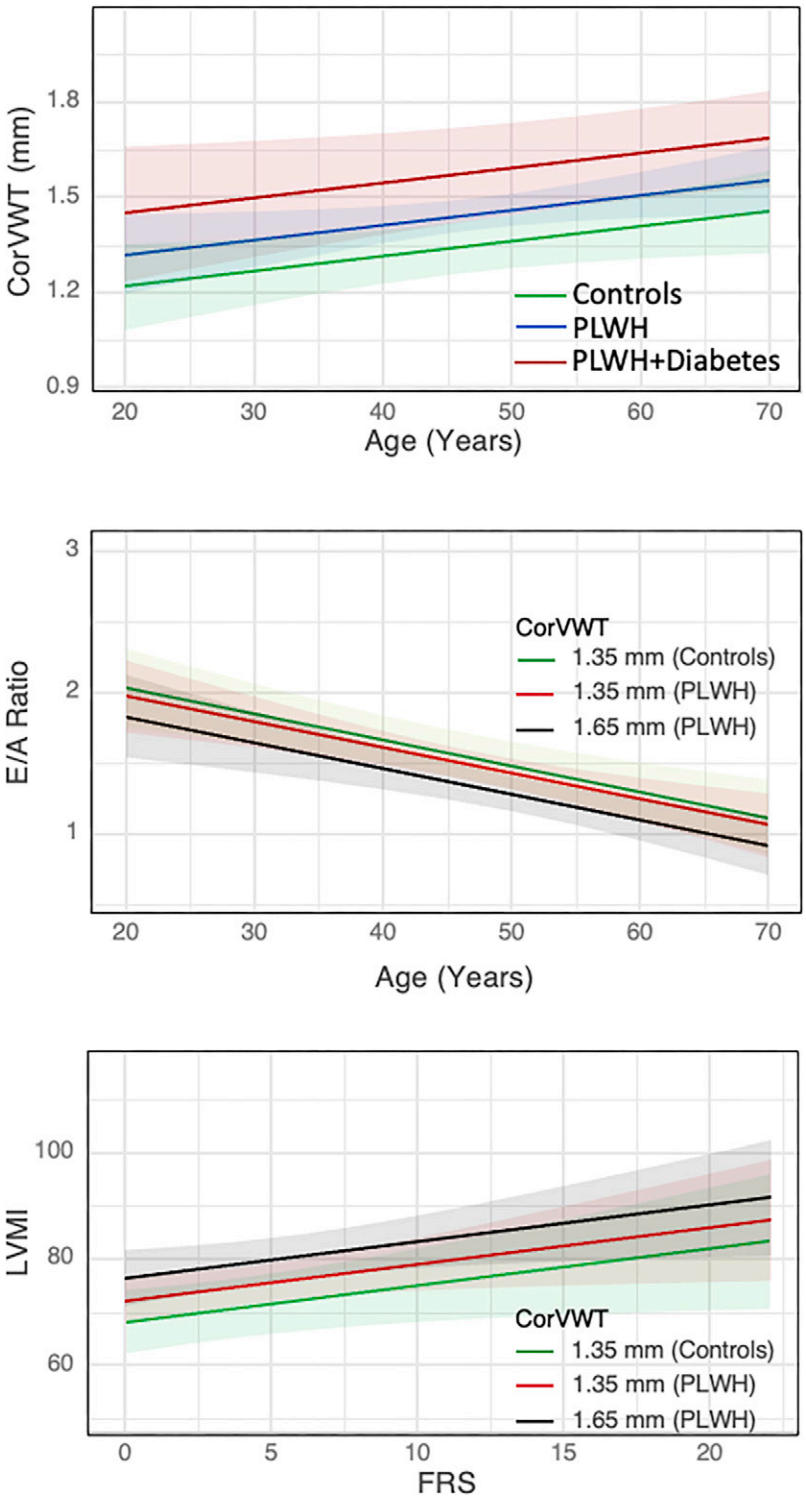

Figure 4: Demonstration of all cohort multiple regression results in Table 3. Top row: Association between coronary artery vessel wall thickness (CorVWT) and age in the control group (green) and the effect of HIV infection (blue) and diabetes (red). Middle row: Relation between E/A (ratio of left ventricular–filling peak blood flow velocity in early diastole (the E wave) to that in late diastole (the A wave) and age in the control group at CorVWT of 1.35 mm (green), in persons living with HIV (PLWH) at the same CorVWT (red), and in PLWH with a thicker CorVWT of 1.65 (black). Bottom: Left ventricular mass index (LVMI) versus Framingham risk score (FRS) in controls at CorVWT of 1.35 mm (black), in PLWH at the same thickness (red), and in PLWH at CorVWT of 1.65 mm (black). The correlation between the years of HIV infection and CorVWT was deemed nonsignificant. Relationships are shown at the mean value of years of HIV infection.

pathology, albeit demonstrating significant heterogeneity (19).

This complex nature of HIV-related cardiovascular abnormalities becomes evident with use of multimodal cardiovascular imaging techniques. Each imaging modality provides distinct insights into the structure, function, and physiology of the heart. For instance, echocardiography is considered the benchmark method for assessing diastolic dysfunction severity (20) and complements MRI. It enables real-time cardiac imaging and provides crucial insights into the dynamics of heart chamber filling and relaxation processes, which are fundamental to diastolic function. Meanwhile, cardiac MRI can provide higher spatial resolution information. Nuclear imaging can facilitate an evaluation of viable myocardial extent in PLWH. By combining the information from different modalities, a more thorough understanding of the disease can be achieved (21–23).

In our investigation, we used echocardiography and MRI, thereby expanding on the established findings and elucidating a noteworthy significant association between diminished diastolic function and increased coronary artery VWT in PLWH. The results suggest further investigation is warranted regarding whether coronary vessel thickening could serve as an indicator of diastolic impairment or lead to a deleterious effect on myocardial function. The findings also underscore the potential utility of coronary artery VWT quantification via MRI as a surrogate metric for detecting subclinical and potentially reversible coronary pathology, as well as identifying plausible causative links with diastolic dysfunction in middle-aged PLWH with low FRS.

Wall thickness was measured for the proximal segment of RCA instead of the left anterior descending artery or left circumflex artery for multiple reasons. In terms of depth, the RCA, being closer to the body's anterior surface, experiences stronger signal acquisition by the imaging coils while concurrently minimizing potential artifacts from motion or flow that might emerge from deeper anatomic locations. A previous study demonstrated the relationship of coronary artery VWT with atherosclerosis by histopathology (15). Nevertheless, the cause of coronary wall thickening in PLWH is multifaceted. As an infectious disease, HIV infection triggers a state of systemic chronic inflammation. This inflammatory response can lead to vascular injury, particularly to the coronary arteries, causing multiple forms of coronary vasculopathies, including HIV-mediated atherosclerosis and vasculitis. Prolonged use of ART has also been documented to correlate with metabolic abnormalities that may lead to CAD

Table 4: Univariable and Multivariable Linear Regression Models in Persons Living with HIV between Candidate Independent Predictors with Coronary Vessel Wall Thickness, E/A, and Left Ventricular Mass Index

	Univariable		Multivariable	
Variable	Coefficient β (SE)	*P* Value	Coefficient β (SE)	*P* Value
Coronary artery VWT (in PLWH)				
Age in years	0.005 (0.002)	.04	...	...
Smoking history in pack-years	0.002 (0.001)	.03	0.002 (0.001)	.02
FRS	0.008 (0.005)	.12	...	...
Diabetes (yes)	0.177 (0.081)	.03	...	...
$CD4^+/CD8^+$ ratio	-0.030 (0.041)	.47	...	...
Duration of HIV infection in years	0.004 (0.003)	.19	...	...
Duration of didanosine use in years	0.032 (0.009)	<.001	0.033 (0.009)	<.001
E/A (in PLWH)				
Age in years	-0.021 (0.004)	<.001	-0.017 (0.004)	<.001
Smoking history in pack-years	-0.002 (0.002)	.25	...	...
FRS	-0.025 (0.01)	.02	...	...
Diabetes (yes)	-0.437 (0.164)	.01	...	...
$CD4^+/CD8^+$ ratio	0.007 (0.088)	.94	...	...
Duration of HIV infection in years	-0.012 (0.007)	.11	...	...
Duration of didanosine use in years	-0.064 (0.019)	.002	-0.037 (0.018)	.05
Coronary artery VWT in mm	-0.818 (0.229)	.001	-0.484 (0.225)	.03
LVMI (in PLWH)				
Age in years	0.396 (0.165)	.02	...	...
Smoking history in pack-years	0.015 (0.075)	.84	...	...
FRS	1.033 (0.335)	.003	1.013 (0.342)	.004
Diabetes (yes)	9.754 (5.768)	.09	...	...
$CD4^+/CD8^+$ ratio	-5.320 (3.001)	.08	...	...
Duration of HIV infection in years	0.612 (0.231)	.02	...	...
Duration of didanosine use in years	1.422 (0.689)	.04	...	...
Coronary artery VWT in mm	17.849 (8.029)	.03	18.271 (8.343)	.03

Note.—E/A = ratio of left ventricular–filling peak blood flow velocity in early diastole (the E wave) to that in late diastole (the A wave), FRS = Framingham risk score, LVMI = left ventricular mass index, PLWH = persons living with HIV, SE = standard error, VWT = artery vessel wall thickness.

(24). Coronary wall thickening might also be consequent to intramural coronary artery changes affiliated with HIV-induced cardiac dysfunction and myopathy, a major cause of morbidity and mortality among PLWH even with the use of ART (25,26).

In addition to the HIV association with elevated coronary artery VWT, our study showed that diabetes had a significant effect on coronary artery VWT. Diabetes is a known CVD risk factor characterized by chronic low-grade inflammation, and its systemic effects include impact on the cardiovascular system, potentially influencing coronary wall thickness (27).

Estimates of diastolic dysfunction prevalence among PLWH range from 8% to 49%, depending on the criteria used to define diastolic dysfunction (9,28–31). Using the 2016 ASE guideline, we identified indeterminate or definite diastolic dysfunction in 13.5% of the present cohort. Butler et al (32) used transthoracic echocardiography to characterize diastolic dysfunction in a cohort of PLWH receiving ART; they demonstrated that PLWH with diastolic dysfunction had increased focal myocardial fibrosis at cardiac MRI. Unlike our study, none of the previous studies investigated the relationship between coronary artery pathology and the functional aspects of the myocardium. However, these studies highlight the prevalence of diastolic abnormalities in PLWH and the multifactorial nature of their cause.

Exposure to abacavir and didanosine may result in acute myocardial damage (33,34), but the specific mechanism remains unclear. Using in vivo studies of rat venules and arterioles and in vitro investigation of human umbilical endothelial cells, De Pablo et al (35) showed enhanced leukocyte adhesion and emigration with exposure to both didanosine and abacavir. Alteration in endothelial leukocyte interactions of this nature may contribute to the observed increased coronary artery VWT in PLWH and its association with the duration of didanosine exposure. Although didanosine is no longer a preferred nucleotide reverse transcriptase inhibitor for the treatment of HIV, PLWH with previous exposure may represent a unique risk group regarding the long-term health effects of this therapy. In addition,

because of didanosine's adverse effects and drug interactions (36), we considered it in the analysis and adjusted for its potential adverse effects.

Tomographic coronary artery VWT measurements are sensitive to both the method and modality of imaging. Multiple factors, such as image resolution, signal-to-noise ratio, blood signal suppression, motion artifacts, and scanning duration, collectively impede adequate visual depiction of the vessel wall and its slight thickness changes during the cardiac cycle. Our approach involved the capture of successive diastolic burst-mode time frames, measurement of multiple continuous wall thickness readings around the lumen perimeter, and automation of vessel wall measurements to uphold objectivity.

TRAPD was used in this study for several compelling reasons. Foremost, it has demonstrated reliability and robustness across numerous studies (10,14,15,37), thus ensuring uniformity and comparability of findings. Recently developed two-dimensional techniques align with the principles of TRAPD, with the exception of use of radial acquisition in place of spiral acquisition (38). Meanwhile, recent three-dimensional advancements (39) necessitate lengthy acquisition periods that are impracticable and intolerable for our patient group and consequently result in reduced resolution, increased motion artifacts, and the necessity of proprietary reconstruction approaches.

In addition to the association with coronary artery VWT, impaired diastolic function and lower coronary pressure may affect coronary lumen size. However, this association was not detected in previous studies among patients with elevated blood pressure and systemic vasoconstriction showing decreased coronary vessel lumen area without VWT (40).

There are more than 20 different transthoracic echocardiographic variables for measuring diastolic function (13), demonstrating at best modest correlation with invasively measured diastolic pressures (41–43). None of these variables adequately captures the complexity of diastolic function, and the final decision is derived through an elaborate multivariable decision tree, often yielding an indeterminate diagnosis with reported accuracies spanning between 56% and 87% (44–47). Although coronary artery vessel wall MRI might not yet be a widely accessible technique, there has been a substantial uptick in the development and adoption of advanced cardiovascular MRI techniques, particularly in efficient three-dimensional and higher-order imaging, as well as automated motion-resolved reconstruction. These developments can further support the ability of MRI to detect early changes in coronary vascular wall thickness, which may signal the onset of diastolic dysfunction not yet evident in echocardiographic measurements. Given the intrinsic limitations of echocardiography, such as challenges in depth perception, resolution, and interpretability, these advancements in the ability of MRI to detect early changes in coronary VWT carry the potential to gain broader prevalence in commercial imaging systems and clinical applications and could potentially enhance diagnostic precision.

Our study had some limitations. The study's cross-sectional nature precludes the identification of causality in the observed associations. Contact with participants has not been sustained, and no return follow-up evaluations have been completed. Although the data presented suggest coronary artery VWT and diastolic dysfunction may have correlation, long-term outcome data must be studied further to address causality. In addition, increased awareness of CVD risk among PLWH and their providers may have contributed to the higher rate of lipid-lowering therapy among PLWH despite similar FRS relative to controls (48,49). Furthermore, although screened for known CVD, the study sample was allowed to self-refer and therefore may not fully represent the general populations of PLWH. Although the study was conducted several years ago, the value and relevance of the study still persist, particularly because the progression and manifestations of HIV and ART on the cardiovascular system are still a clinical challenge. The heterogeneity of the effect of HIV on CVD and the role of multimodality imaging is still not fully established. The information gained from these data about the association between coronary thickening measured with MRI and diastolic function impairment measured with echocardiography has not been discussed before and can serve as foundational knowledge on which more recent studies can build.

In conclusion, middle-aged PLWH with low FRS and without established CVD had increased coronary artery VWT in association with evidence of impaired diastolic function; however, direct causality cannot be drawn in this observational study. Coronary artery VWT at MRI may be particularly useful in this middle-aged asymptomatic PLWH and permits early recognition of coronary artery pathology in this population. Coronary artery VWT may be amenable to follow-up studies of pathogenesis, which would aid in identifying downstream effects on myocardial function and risk modification strategies.

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