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Circulating levels of cardiac troponin T are associated with coronary noncalcified plaque burden in HIV-infected adults: a pilot study

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Abstract

HIV infection and/or antiretroviral therapy may increase the risk of subclinical coronary atherosclerosis. However, patients with chronic kidney disease (CKD) and those without IV access cannot undergo contrast-enhanced coronary CT angiography (CCTA). This study was to explore the relationship between cardiac troponin T (cTnT) levels and the extent of coronary plaque burden, as assessed by CCTA in those with HIV infection. Between June and September 2017, 58 HIV-infected participants were recruited and underwent contrast-enhanced CCTA. cTnT was measured with the Elecsys Troponin T Gen 5 STAT assay, and noncalcified plaque burden was quantified using coronary plaque analysis. Robust regression model was employed to perform primary statistical analysis. Univariate robust regression analysis indicated that male gender, cardiovascular risk score defined by the 2013 ACC/AHA cardiovascular risk score algorithm, and cTnT levels were significantly associated with noncalcified plaque volume index (NCPI). Final robust regression analyses showed that only cTnT (log scale) was independently associated with the NCPI (regression coefficient: 0.0453 with 95% CI: 0.0151, 0.0755, $p = 0.003$). These results of this study suggest that cTnT may be a promising marker for coronary plaque burden, especially in patients with HIV-associated CKD or without IV access.

Keywords

Noncalcified plaque volume; cardiac troponin T; chronic kidney disease; contrast-enhanced coronary CT angiography; injection drug use; HIV infection

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Statement of Ethics

The Johns Hopkins School of Medicine Institutional Review Board approved the study protocol and consent form, and all study participants provided written informed consent. All procedures used in this study were in accordance with institutional guidelines.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Introduction

As the age of people living with HIV has been rising steadily due to the success of antiretroviral therapy (ART), HIV-associated comorbidities have become the leading cause of mortality for persons living with HIV infection.¹

Since 2004, we have conducted a study to investigate the effects of long-term ART exposure and chronic cocaine use on HIV-associated subclinical coronary atherosclerosis in approximately 980 study participants with HIV infection, with/without ART exposure, and with/without cocaine use, in Baltimore, Maryland.^{2–9} Subclinical coronary atherosclerosis was assessed using contrast-enhanced coronary CT angiography (CCTA). Over the follow-up period from 2004 through 2017, the development and progression of coronary plaque could not be assessed in more than 10% of the study participants as close to 8% of participants developed HIV-associated chronic kidney disease (CKD) precluding CCTA, and IV access for contrast administration failed to be established in 5% of the participants with cocaine addiction. Therefore, a biomarker is needed to monitor coronary plaque progression, especially noncalcified plaque progression in those with HIV-associated CKD or in injection drug users who have difficult IV access for contrast administration. Cardiac troponin T (cTnT) is recognized as a sensitive biomarker of myocardial injury associated with death, myocardial infarction, and heart failure in patients with coronary artery disease (CAD) and pre-served systolic left ventricular function.^{10–17} It was reported that in patients suspected of having CAD without acute coronary syndrome, progressively increasing cTnT levels were found in patients with mild lesions (<50%), moderate lesions (50–75%), and severe lesions (>75%), compared to levels in patients without CAD (all $p < 0.01$).¹⁸ Furthermore, the association between elevated cTnT and significant coronary stenosis is not influenced by renal function.¹⁹ The objective of this investigation was to explore whether cTnT is associated with noncalcified plaque burden in those with HIV infection.

Methods

Participants

Between June and September 2017, a total of 58 HIV-infected adult participants who had undergone contrast-enhanced CCTA were recruited from our ongoing study, exploring whether cTnT is associated with noncalcified plaque burden. Of the 58 participants, eight had undergone contrast-enhanced coronary CCTA previously, but were diagnosed with CKD at enrollment of this study, 11 had no apparent coronary stenosis, as defined as all coronary stenosis <20%, 21 had coronary stenosis between 20 and 50%, and 18 had >50% coronary stenosis.

Inclusion criteria were (1) age ≥ 21 years; (2) HIV positivity, as determined by ELISA and confirmed by Western blot test; and (3) cocaine use: defined as use by any route for at least six months, administered at least four times/month. Infrequent users (fewer than four times/month, or <6 consecutive months) were not recruited. Chronic cocaine users who also used other drugs such as opiates or alcohol were included. Non-cocaine use was defined as never used cocaine or not used in the past five years or longer, assessment of cocaine use was based on self-reported use. Exclusion criteria were (1) any evidence of clinical CAD or any

history of or current symptoms or diagnoses related to cardiovascular disease; (2) history of serious physical disease or current physical disease including chronic obstructive pulmonary disease; (3) pregnancy; (4) CKD with an estimated glomerular filtration rate (eGFR) of < 60 ml/min/1.73 m²; and (5) contraindication to CT scans, including a history of contrast allergy.

Main procedures

Interview, medical chart review, physical and laboratory examination.—During the baseline visit, study participants underwent a detailed interview to obtain information about sociodemographic characteristics, medical history, behaviors, including alcohol consumption, drug use, cigarette smoking, and medications. Detailed information about HIV-related risk factors, duration of known HIV infection, and medications, including ART use, was also collected. A medical chart review was used to confirm the information on medical history and medications provided by the study participants. A physical examination was performed and vital signs were recorded. Routine clinical laboratory blood chemistry tests were conducted. The following laboratory tests were performed: eGFR, total serum cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), glucose, and high-sensitivity C-reactive protein (hs-CRP).

cTnT measurement.—Blood samples were drawn from a peripheral vein approximately 2 h before the CT angiography scan. Samples were stored immediately at –80°C and were stored until analysis. Thus, the radiologists and technician who analyzed plaque volume index did not know the cTnT values.

The cTnT values were measured in heparinized plasma with the Elecsys Troponin T Gen 5 STAT assay on the cobas e 411 immunoassay analyzer (Roche Diagnostics, Indianapolis, IN).

The assay is specific for cTnT without relevant interferences and has an analytic range of 6–10,000 ng/l (defined by the limit of quantitation and the maximum of the master curve). Values below 6 ng/l are reported as < 6 ng/l. Values above the measuring range are reported as > 10,000 ng/l (or up to 100,000 ng/l for ten-fold diluted samples). The Elecsys Troponin T Gen 5 STAT assay does not show any significant cross-reaction with the following substances (tested with cTnT concentrations of approximately 14, 4000, and 7000 ng/l). The 99th percentile upper reference limits were determined to be 19 ng/l for both genders, 14 ng/l for females, and 22 ng/l for males (<https://usdiagnostics.roche.com/products/07398000160/PARAM204/overlay.html>).

Contrast-enhanced CCTA.—Cardiac CT scans were performed on a Siemens second-generation, 128-slice, dual-source CT (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany). No premedication was used. After a test bolus application to optimize the acquisition timing for the participant (10 cc bolus of contrast), CT angiography was performed. The scan parameters were 100–120 kVp (depending on the patient's size), Care Dose quality reference standard of 320 mA s (Care Dose 4D was used to minimize radiation dose), rotation time was 0.28 s, collimation was 128 mm × 0.6 mm, and average acquisition time was under 5 s (heart rate dependent). Scan data were reconstructed with .75 mm thickness at .5 mm reconstruction spacing using a B26ASA and B30f reconstruction

kernel with iterative reconstruction. The scan protocol used 80–100 ml of an isoosmolar contrast agent (Vispaque-320, GE Medical Systems) injected at 5–6 cc/s. Images for calcium scoring were obtained precontrast (120 kVp, 3 mm slice thickness).

CCTA volumetric plaque analysis.—Plaque analysis was performed independently in the Department of Radiology and Imaging Sciences, National Institutes of Health Clinical Center with the use of the QAngioCT software (Research Edition, version 2.0.5; Medis Medical Imaging Systems, Leiden, the Netherlands). The software has been validated against IVUS²⁰ and was used extensively in clinical studies.^{21–24}

The image analysts were blinded to participants' characteristics. The coronary tree was automatically extracted, and each of the major vessels (i.e. the left anterior descending artery, the left circumflex artery, and the right coronary artery) was individually analyzed from the ostium to the point at which the internal vessel caliber decreased to < 2.0 mm, exclusive of focal stenosis. Segmentation was performed according to AHA nomenclature.²⁵ Segments with image artifacts or stents were excluded. Automated longitudinal contouring of the inner lumen and outer wall was performed and results were manually adjusted when clear deviations were noted. Results of automated contouring of the inner lumen and outer wall were also reviewed on transverse reconstructed cross-sections of the artery on a section-by-section basis at 0.5 mm increments.²¹ Lumen attenuation was adaptively corrected on an individual scan basis by using gradient filters in combination with the intensity values in the arteries, allowing for comparison between data sets.²⁰ Total plaque volume (calcified plus noncalcified plaque volume) was calculated by subtracting the lumen volume from the outer wall volume. The plaque burden per unit length was calculated as segmental plaque volume (in mm³)/length (in mm) of the corresponding segment, yielding the total plaque volume index (in mm²); noncalcified plaque volume index (NCPI) was calculated as the total volume index minus the calcified plaque volume index (in mm²).²¹

Statistical analysis

Statistical analysis was performed with SAS (SAS 9.4, SAS Institute, Cary, NC). All continuous parameters were summarized by medians (interquartile range), and all categorical parameters were summarized as proportions. The data for this investigation included sociodemographic characteristics, medical history, behaviors, including alcohol consumption, drug use, cigarette smoking, medications, laboratory and imaging parameters, some of which may not be normally distributed and inevitably contain 'outliers.' Robust regression model with the least trimmed squares (LTS) estimation method was used to provide robust results in the presence of outliers.²⁶ Robust regression is an alternative form of regression analysis that is robust or stable with respect to violations of assumptions for ordinary least squares regression procedures. Robust regression analysis was performed on log-transformed (the natural log transformation) cTnT. Univariate robust regression models were first fitted to evaluate the crude associations between NCPI and each individual factor, including age, gender, cigarette smoking, alcohol consumption, BMI, hs-CRP, blood pressure, eGFR, fasting glucose, total cholesterol, LDL, HDL, triglycerides, ACC/AHA cardiovascular risk score,²⁷ years since HIV infection was diagnosed, the nadir CD4 cell count (defined as the lowest CD4 cell count after HIV infection was diagnosed), the first

CD4 cell count when HIV was diagnosed, CD4 cell count at baseline, the first HIV viral load level (log-transformed) when HIV was diagnosed, the highest HIV viral load level (log-transformed) since HIV was diagnosed, HIV viral load level (log-transformed) at baseline, months of nucleoside reverse transcriptase inhibitors use, months of nonnucleoside reverse transcriptase inhibitors use, and months of protease inhibitors use. Those factors that were significant at the $p < 0.05$ level in the univariate models were put into the multivariate robust regression models to investigate the joint effect of these factors on NCPI. Those variables that ceased to make significant contributions to the models based on these two criteria were deleted in a stagewise manner, and a new model was refitted. This process of eliminating, refitting, and verifying continued until all of the variables included were statistically significant, yielding a final model. The p-values reported are two-sided, and $p < 0.05$ indicates statistical significance.

Results

General characteristics

General characteristics of the study participants are presented in Table 1. Among the 58 participants, eight were diagnosed with CKD at enrollment and their most recent CCTA image data obtained prior to the CKD diagnosis were used for the analysis. Of the 58 participants in this study, 42 (72.4%) were male. Their mean age was 57.1 (± 5.1) years, and 51 (87.9%) were cigarette smokers and chronic cocaine users. The median (interquartile range) of cTnT was 10.28 (8.19–4.04) ng/l. According to the 2013 ACC/AHA cardiovascular risk score algorithm,²⁶ 11 (19.0%) of the study participants had a low risk of CAD. The mean BMI was 27.6 (± 6.0) kg/m². The mean NCPI was 0.86 (± 0.17) mm².

Factor(s) associated with NCPI

Univariate robust regression analysis indicated that male sex, ACC/AHA cardiovascular risk score,²⁷ and cTnT levels were significantly associated with the NCPI (Table 2). The final robust regression analysis showed that only cTnT was independently associated with NCPI (Table 2).

A scatterplot suggests that cTnT level was positively associated with NCPI (R^2 based on the LTS estimation method = 0.10, $p = 0.0035$) (Figure 1).

Discussion

In this study, we found that cTnT levels were independently associated with NCPI in persons with HIV infection.

It was reported that HIV infection is significantly associated with an increased prevalence of coronary plaque volume in young, asymptomatic, HIV-infected men with long-standing HIV disease.²⁸ A large metaanalysis investigating whether there is an increased prevalence of, or structural changes in, coronary artery plaques in asymptomatic HIV patients demonstrated that compared to those without HIV infection, asymptomatic HIV patients present a similar burden of coronary stenosis and calcified coronary artery plaques but significantly higher rates of noncalcified coronary plaques on computed tomography.²⁹ Noncalcified plaques

represent an early stage of atherosclerosis and are considered more vulnerable and prone to rupture than calcified plaques, which are viewed as more stable.^{30–34}

With the advent of ART, long-term cardiac risk in HIV-infected patients is primarily related to arterial disease, specifically atherosclerosis, and to a much lesser extent to the myocardium, the source of cTnT.³⁵ HIV infection was shown to be associated with subclinical regional left ventricular systolic and diastolic dysfunction in individuals free of overt cardiovascular disease.³⁶

Compared to HIV uninfected, those with HIV infection have a higher prevalence of left ventricular hypertrophy diastolic dysfunction that is not explained by hypertension or other reasons.^{37,38} Various reasons for elevated cTnT levels in HIV-infected patients including fibrosis and inflammation/virus-related myocardial damage have already been described.^{39,40}

Coronary plaque may rapidly progress in cocaine users. The incidence of coronary plaque progression in cocaine users was 7.4/100 person-years and 23.1/100 person-years in those who were totally abstinent from cocaine and those who continued to use cocaine, respectively.⁴¹ In a preliminary study, we found that, on average, noncalcified plaque volume in cocaine users increased 50 mm³ per year.⁴² cTnT is the biomarker of choice for the diagnosis of myocardial injury, because it is the most sensitive and cardiac-specific laboratory measure of myocardial injury currently available.^{43–46} Although cTnT was reported to be associated with coronary lesions,¹⁸ the association between cTnT levels and noncalcified plaque volumes in those with HIV infection has not been reported. One of the purposes of this study was to explore whether cTnT could be used as a biomarker for the extent of coronary plaque burden in those with HIV infection and HIV-associated CKD since these patients cannot undergo contrast-enhanced CT angiography. It was reported that the association between elevated high-sensitivity cTnT and significant coronary stenosis is not influenced by renal function.¹⁹

A recent study demonstrated that advanced HIV infection (CD4 < 200/mm³) was associated with a high risk of soft plaques and with a worse prognosis, including cardiovascular events and acute coronary syndrome recurrence, suggesting that highly replicating virus may lead to a higher risk of more unstable plaque.⁴⁷ In contrast, this study did not include any participant with advanced HIV disease. The difference in HIV disease stage may explain why the alleged association between CD4 and noncalcified plaque was not identified in our study.

There are some potential major limitations of this study, which merit discussion. First, the sample size of this study is small. Large studies will be needed to confirm the findings of this investigation. Second, since this investigation is a cross-sectional study, we cannot examine changes in cTnT in relation to changes in noncalcified plaque volume. Longitudinal studies will be needed to examine whether changes in cTnT are associated with changes in noncalcified plaque volume. Third, due to the nature of the cross-sectional design, any hidden confounding factors could not be adjusted for. Fourth, the participants enrolled in this study were heterogeneous with regard to their cardiac risk. This study failed to include a

control group due to small sample size. Lastly, due to selection bias (the majority of our study participants were cocaine users), this study failed to identify the impact of cocaine use on cTnT.

Conclusions

The findings of this study demonstrated that high-sensitivity cTnT is independently associated with noncalcified plaque volume. If these findings are confirmed by large studies, cTnT may be used as a biomarker for the presence and extent of coronary plaque in patients with HIV and CKD or other conditions precluding IV contrast administration.

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Figure 1. Scatterplot of NCPI versus cTnT. The y-axis corresponds to NCPI (in mm^2), while the x-axis corresponds to cTnT levels (in ng/l). The correlation coefficient between NCPI and cTnT was 0.10 ($p=0.0035$). NCPI: noncalcified plaque volume index.

Table 1.Characteristics of 58 HIV-infected participants.^a

Characteristic	N = 58
Age (years)	56 (53–61)
Male gender (%)	72.4
Family history of heart attack (%)	29.3
Cigarette smoking (%)	87.9
Cocaine use (%)	87.9
Alcohol use (%)	89.7
Hypertension (%)	17.2
Diabetes (%)	10.3
BMI (kg/m ²)	27.6 (23.6–31.7)
Systolic BP (mm Hg)	129 (114–136)
Diastolic BP (mm Hg)	74 (66–81)
eGFR (ml/min/1.73 m ²)	91 (81–111)
hsCRP (mg/dl)	2.6 (0.7–6.6)
Glucose (mg/dl)	88 (80–96)
Total cholesterol (mg/dl)	170 (147–195)
LDL-C (mg/dl)	82 (65–101)
HDL-C (mg/dl)	60 (43–72)
Triglycerides (mg/dl)	115 (90–160)
Significant stenosis (%)	34.5
The 2013 risk (%)	14.2 (8.1–20.2)
Low 2013 risk	19.0
Years since HIV was diagnosed	19.6 (12.4–23.8)
CD4 nadir (cells/mm ³)	220 (167–315)
CD4 at baseline (cells/mm ³)	490 (376–590)
Maximum HIV RNA (copies/ml), log ₁₀ scale	4.40 (4.10–5.56)
HIV RNA at baseline (copies/ml), log ₁₀ scale	1.49 (1.30–2.58)
ART use (%)	65.5
NRTI use (%)	51.7
NNRTI use (%)	24.1
PI use (%)	36.2
Abacavir use (%)	1.72
Months of ART use	48.4 (0.1–128.1)
Months of NRTI use	3.40 (0.1–96.0)
Months of NNRTI use	0.1 (0.1–0.1)
Months of PI use	0.1 (0.1–48.7)
cTroponin T (ng/l), log scale	2.33 (2.10–2.64)
Total coronary plaque volume index (mm ²)	0.93 (0.81–1.14)
Total calcified plaque volume index (mm ²)	0.07 (0.02–0.25)

Characteristic	N = 58
Total noncalcified plaque volume index (mm ²)	0.82 (0.76–0.92)

ART: antiretroviral therapy; BMI: body mass index (kg/m²); BP: blood pressure; CD4 nadir: the lowest CD4 cell count recorded; cTroponin T: cardiac troponin T; eGFR: estimated glomerular filtration rate; glucose: fasting glucose; HDL-C: high density lipoprotein cholesterol; hsCRP: high-sensitivity C-reactive protein; LDL-C: low density lipoprotein cholesterol; low 2013 risk: the 2013 risk < 0.075%²⁷; maximum HIV RNA: the highest HIV viral load level recorded; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; the 2013 risk: cardiovascular risk defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk.²⁷

^aMedian (interquartile range) for continuous variables, proportion (%) for categorical variables.

Table 2.

Factors associated with noncalcified plaque volume index, robust regression analyses.

Characteristic	Univariate model Regression coefficient (95%CI) p-value	Initial multivariate model Regression coefficient (95%CI) p-value	Final multivariate model Regression coefficient (95%CI) p-value
Age (years)	0.0064 (−0.0004, 0.0132) 0.07		
Male gender (%)	0.0831 (0.0122, 0.1540) 0.02	0.0399 (−0.0243, 0.1042) 0.22	
Cigarette smoking	−0.0185 (−0.0989, 0.1005) 0.99		
Cocaine use	0.0008 (−0.1001, 0.0969) 0.97		
Alcohol use	−0.0132 (−0.1129, 0.0864) 0.79		
BMI (kg/m ²)	0.0043 (−0.0008, 0.0094) 0.10		
Systolic BP (mm Hg)	0.0004 (−0.0015, 0.023) 0.68		
Diastolic BP (mm Hg)	0.0026 (−0.0001, 0.0053) 0.06		
hsCRP (mg/dl)	0.0016 (−0.0025, 0.0058) 0.44		
eGFR (ml/min/1.73 m ²)	−0.0008 (−0.0021, 0.0005) 0.23		
Glucose (mg/dl)	0.0009 (−0.0007, 0.0024) 0.26		
Total cholesterol (mg/dl)	−0.0001 (−0.0009, 0.0007) 0.83		
LDL-C (mg/dl)	0.0004 (−0.0005, 0.0012) 0.39		
HDL-C (mg/dl)	−0.0014 (−0.0030, 0.0002) 0.08		
Triglycerides (mg/dl)	−0.0000 (−0.0005, 0.0005) 0.98		
Significant coronary stenosis (%)	0.0562 (0.0118, 0.1241) 0.11	0.2868 (−0.0948, 0.6683) 0.14	
The 2013 risk (%)	0.5535 (0.2046, 0.9023) 0.0019		
Low 2013 risk (%)	−0.0678 (−0.1485, 0.0130) 0.10		
Years since HIV was diagnosed	0.0009 (−0.0033, 0.0051) 0.69		
CD4 nadir (cells/mm ³)	0.0000 (−0.0004, 0.0005) 0.87		
CD4 at baseline (cells/mm ³)	0.0000 (−0.0001, 0.0001) 0.51		
Maximum HIV RNA (copies/ml), log ₁₀ scale	−0.0089 (−0.0633, 0.0456) 0.75		
HIV RNA at baseline (copies/ml), log ₁₀ scale	0.0100 (−0.0158, 0.0358) 0.45		
Months of ART use	0.0002 (−0.0001, 0.0005) 0.21		
Months of NRTI use	0.0003 (−0.0001, 0.0007) 0.13		
Months of NNRTI use	0.0002 (−0.0005, 0.0009) 0.65		
Months of PI use	0.0001 (−0.0004, 0.0005) 0.76		

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Characteristic	Univariate model Regression coefficient (95%CI) p-value	Initial multivariate model Regression coefficient (95%CI) p-value	Final multivariate model Regression coefficient (95%CI) p-value
cTroponin T (ng/l), log scale	0.0453 (0.0151,0.0755) 0.003	0.0277 (−0.0066, 0.0620) 0.11	0.0453 (0.0151,0.0755) 0.003

ART: antiretroviral therapy; BMI: body mass index (kg/m²); BP: blood pressure; CD4 nadir: the lowest CD4 cell count recorded; cTroponin T: cardiac troponin T; eGFR: estimated glomerular filtration rate; glucose: fasting glucose; HDL-C: high density lipoprotein cholesterol; hsCRP: high-sensitivity C-reactive protein; LDL-C: low density lipoprotein cholesterol; low 2013 risk: the 2013 risk < 0.075%²⁷; maximum HIV RNA: the highest HIV viral load level recorded; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; the 2013 risk: cardiovascular risk defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk.²⁷