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Biomarkers and Electrocardiographic Evidence of Myocardial Ischemia in Patients With Human Immunodeficiency Virus Infection

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Abstract

We assessed the relation of inflammatory and coagulation biomarkers with electrocardiographic (ECG) evidence of myocardial ischemia. High-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and D-dimer levels were measured at study entry for 3,085 human immunodeficiency virus-infected participants (mean age 44 years; 26.4% women; 24.6% black) in the Strategies for Management of Antiretroviral Therapy trial. Logistic regression models were used to examine the associations of these biomarkers with prevalent and incident myocardial ischemia. The latter analyses were performed for 1,411 participants who were randomly assigned to receive continuous antiretroviral therapy during follow-up to suppress the human immunodeficiency virus viral load and had ≥1 ECG reading during the follow-up period. The median hsCRP, IL-6, and D-dimer level was 1.65 μg/ml (interquartile range 0.69 to 4.11), 1.60 pg/ml (interquartile range 1.00 to 2.75), and 0.18 μg/ml (interquartile range 0.11 to 0.32), respectively. At baseline, the prevalence of major or minor Q-QS or ST-T ECG abnormalities was 18.6%. The biomarker levels were associated with prevalent major or minor ischemic abnormalities on the univariate analyses; however, adjustment for traditional risk factors attenuated these associations. The adjusted odds ratio for major or minor ischemic abnormalities and 95% confidence intervals for the greatest versus lowest quartiles was 1.3 (95% confidence interval 0.9 to 1.7) for hsCRP, 1.0 (95% confidence interval 0.7 to 1.3) for IL-6, and 1.1 (95% confidence interval 0.9 to 1.5) for D-dimer. During a median follow-up of 2.3 years, new definite or probable ischemic ECG abnormalities developed in 11.7% of participants receiving continuous antiretroviral therapy. Biomarker levels were not associated with incident abnormalities on unadjusted or adjusted analyses. In conclusion, higher levels of hsCRP, IL-6, and D-dimer were

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Supplementary data

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not associated with ischemic ECG abnormalities. Elevated biomarker levels and ECG abnormalities indicating myocardial ischemia might reflect different risk pathways for cardiovascular disease.

After completion of the Strategies for Management of Antiretroviral Therapy (SMART) trial,[1] the acute-phase reactant high-sensitivity C-reactive protein (hsCRP), the proinflammatory cytokine interleukin-6 (IL-6), and the coagulation marker, D-dimer, were measured from stored baseline specimens. These baseline biomarker levels predicted cardiovascular disease (CVD) and all-cause mortality[1,2] and were higher compared to the general population, even among participants taking antiretroviral therapy and with human immunodeficiency virus (HIV) RNA <400 copies/ml.[3] The elevation of these biomarkers, even with successful treatment of HIV, has been attributed to persistent chronic immune activation.[4] Similar to studies of the general population,[5,6] the presence of a major electrocardiographic (ECG) abnormality at baseline in the SMART trial was associated with developing CVD.[7] We hypothesized that the severity of the chronic proinflammatory state evident during treated HIV infection, as measured by these 3 biomarkers, would be associated with a greater prevalence of ischemic ECG abnormalities at baseline and a greater incidence of ischemic abnormalities during follow-up among participants receiving continuous antiretroviral therapy and without evidence of clinical CVD.

Methods

The study design, methods, and primary results of the SMART study have been previously reported (ClinicalTrials.gov identifier: NCT00027352).[8] In brief, 5,472 HIV-infected participants with baseline CD4-positive T-cell counts ≥350 cells/mm^3 were randomized to receive either continuous antiretroviral therapy (viral suppression arm; n = 2,752) or CD4-positive T-cell count—guided antiretroviral therapy (drug conservation arm; n = 2,720).

For the cross-sectional analyses, we focused on 3,085 participants with baseline biomarker data and a 12-lead electrocardiogram at rest who were receiving antiretroviral therapy at study entry, had a plasma HIV RNA level of ≥400 copies/ml, and did not have a history of CVD (previous myocardial infarction, stroke, or coronary artery disease requiring surgery or drug treatment or a history of stroke, peripheral vascular disease, or congestive heart failure). For the longitudinal analyses, we further restricted our analysis to 1,411 participants with ≥1 follow-up electrocardiogram at rest, who were randomized to continuous antiretroviral therapy (viral suppression group) because these participants reflect the current standard of care for HIV.

The biomarkers, hsCRP, IL-6, and D-dimer, were studied, because they were shown to be strongly related to all-cause mortality and CVD clinical outcomes in the SMART study and because they were centrally measured from stored plasma for all consenting participants.[1,2] IL-6 was measured using the chemiluminescent sandwich enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minnesota); hsCRP using the NM II nephelometer, N Antiserum to Human CRP (Siemens Diagnostics, Deerfield, Illinois); and D-dimer levels using immunoturbidometric methods on the Sta-R analyzer, Liatest D-DI (Diagnostica Stago, Parsippany, New Jersey). The institutional review board at the University of Minnesota approved the plans for the analysis of the stored specimens.

An electrocardiogram at rest was recorded at baseline and the annual visits. The standard protocol used by all clinical sites for the collection of standard 12-lead electrocardiograms at rest in the SMART study has been previously described.[7] Prevalent ECG abnormalities and the development of incident myocardial ischemia were classified using the Minnesota Code ECG classification.[5,9] Prevalent ECG abnormalities were grouped into major or any (major

or minor) ischemic abnormalities. Major abnormalities were defined as the presence of major Q-QS or major ST-T abnormalities. Minor abnormalities were defined as presence of isolated minor Q-QS or isolated minor ST-T abnormalities in the absence of any major ischemic abnormalities (Supplemental Table 1). Definite incident myocardial ischemia was defined as a change from no or less severe myocardial ischemia to more severe myocardial ischemia, reflected as a change in the severity of the Minnesota Code plus an ≥50% to 100% change in the duration or amplitude of the Q/ST-T waves. Probable incident myocardial ischemia was defined as new or worsening of an existing myocardial ischemia, but not a 50% to 100% change in the duration or amplitude of the Q/ST-T waves (Supplemental Table 2).

We used logistic regression models to study the associations of hsCRP, IL-6, and D-dimer with the prevalent ischemic ECG abnormalities. Odds ratios (ORs) were used to compare the risk of an ECG abnormality in patients with a biomarker level in the greatest quartile relative to the lowest, and p values correspond to a 1 SD higher level of the log-transformed biomarker to standardize the interpretation of the relative strength of the associations. ORs are presented unadjusted and adjusted for age, gender, race, baseline body mass index, smoking history, ratio of total cholesterol to high-density lipoprotein, diabetes, blood pressure-lowering medication use, lipid-lowering medication use, abacavir use history, protease inhibitor history, CD4-positive T-cell count at study entry, and hepatitis B and C co-infection.

The number of annual ECG assessments varied among the participants because of the rolling enrollment over several years. Therefore, we used conditional logistic regression models stratified by the number of ECG assessments to examine the association between the baseline biomarker values and the incident ischemic ECG changes. We also fit a Cox model for discrete failure time (annual ECG measurements) that took into account the follow-up visit at which the ECG abnormality was first observed in computing the ORs. Data were analyzed using Stata, version 12.1 (StataCorp, College Station, Texas).

Results

The average age of the 3,085 participants was 44 years (interquartile range 38 to 50); 813 (26%) were women, and 755 (25%) were black. The median CD4-positive T-cell count was 650 cells/mm^3 (interquartile range 497 to 846), 1,162 (38%) were current smokers, the median body mass index was 25 kg/m^2 (interquartile range 22 to 28), the median total cholesterol was 198 mg/dl (interquartile range 171 to 229), and the median high-density lipoprotein level was 42 mg/dl (interquartile range 34 to 52). The median duration of antiretroviral therapy was 4 years (interquartile range 3 to 5).

The median hsCRP, IL-6, and D-dimer level at study entry was 1.65 μg/ml (interquartile range 0.69 to 4.11), 1.60 pg/ml (interquartile range 1.00 to 2.75), and 0.18 μg/ml (interquartile range 0.11 to 0.32), respectively.

Major abnormalities were present in 5.9% of the 3,085 participants, and 19% had at least a major or minor abnormality (i.e., any ECG abnormality; Table 1). Most of the abnormalities were isolated ST-T (14.3% of the participants). The biomarker levels were greater among those with major or minor ischemic abnormalities than in those with no abnormalities (Table 1), and these associations were significant in the unadjusted analyses (Table 2). However, none of the biomarkers remained significantly associated with the presence of ischemic ECG abnormalities after covariate adjustment (Table 2).

Analyses of individual covariates suggested that log-transformed biomarker levels correlated positively with age (all $p < 0.001$), which was the factor that primarily led to the attenuation.

The age-adjusted OR of the presence of any ECG abnormality (major or minor) for the greatest versus lowest quartiles was 1.3 (95% confidence interval 1.0 to 1.7), 1.1 (95% confidence interval 0.8 to 1.4), and 1.3 (95% confidence interval 1.0 to 1.8) for hsCRP, IL-6, and D-dimer, respectively.

For the 1,411 viral suppression participants, the follow-up ECG recordings were 87% complete (2,874 of 3,320 completed). The viral suppression participants had a median of 2 follow-up ECGs (interquartile range 1 to 3) during a median follow-up of 2.3 years. Of the 1,411 participants, 97 (6.9%) had a definite incident ECG change indicative of myocardial ischemia (8 were silent myocardial infarctions), 68 (4.8%) had a probable change, and 165 (12%) had either a definite or probable change in Q-QS or ST-T waves (Table 1). About 92% of the incident definite ECG changes were ST-T abnormalities, and 88% of the probable changes were Q-QS changes.

The biomarker levels were greater for those in the viral suppression arm who developed ischemic abnormalities (Table 1), but none of the associations achieved statistical significance (Table 2). Covariate adjustment further attenuated the strength of the associations.

To determine whether the suppressed Minnesota Codes of ischemia (i.e., codes that should have been present but were not shown because of the presence of other ECG abnormalities) were affecting our results, we performed sensitivity analyses excluding 49 participants (1.6%) in the analysis of prevalent abnormalities and 30 (1.9%) in the analysis of incident abnormalities with QRS of ≥120 ms; however, this had no affect on our results. Similarly, analyses using survival methods did not change our findings (data not shown).

Of the 1,411 participants, 19 (1.3%) experienced a clinical myocardial infarction, had coronary artery disease requiring an invasive procedure diagnosed, or died from CVD during follow-up. Of these 19 participants, 10 (53%) had a definite or probable serial ECG change that preceded the event. Consistent with a previous report,[1] the median hsCRP, IL-6, and D-dimer levels were greater among those who developed clinical CVD (2.45 μg/ml, 2.83 pg/ml, and 0.26 μg/ml, respectively) compared to those who did not (1.61 μg/ml, 1.56 pg/ml, and 0.18 μg/ml, respectively). The levels for the 10 participants who developed CVD and had an ischemic ECG abnormality before the event and for the 9 who developed CVD with a previous ischemic ECG abnormality, were similarly elevated (2.74 μg/ml, 2.83 pg/ml, and 0.22 μg/ml vs 2.13 μg/ml, 2.84 pg/ml, and 0.38 μg/ml for hsCRP, IL-6, and D-dimer, respectively).

Discussion

This is the first study of the relation between hsCRP, IL-6, and D-dimer levels and ECG abnormalities in HIV-infected participants. We aimed to determine whether these biomarkers, which are associated with clinical CVD, also led to an early risk of subclinical CVD as measured by ischemic abnormalities on the electrocardiogram. We found that the prevalence of baseline ECG abnormalities indicative of cardiac ischemia increased with greater biomarker levels; however, after adjustment for age and other risk factors, none of the associations remained significant. Similarly, those who developed incident ECG abnormalities had greater baseline biomarker levels than those who did not, but associations were not significant on either unadjusted or adjusted analysis.

Data on the relation between inflammatory biomarkers and ECG abnormalities in the general population are limited. Asselbergs et al[10] found that the hsCRP levels were greater among participants with than in those without ECG abnormalities on univariate analysis; however, similar to our study, the association was reduced after adjusting for age and

gender. Okin et al[11] demonstrated that hsCRP and ST-segment depression on the electrocardiogram have complementary and additive effects on mortality because of atherosclerosis: elevated hsCRP and ST-segment depression independently predicted CVD mortality, and combining both variables improved the risk stratification compared to either variable alone.[11] In a cross-sectional investigation of the Health, Aging and Body Composition Study in older adults, Cesari et al[12] found that IL-6 and hsCRP were both significantly associated with clinical CVD, but hsCRP was not associated with several subclinical measures of CVD, including ECG abnormalities that included ischemic and other ECG abnormalities. As already noted, in previous reports, we demonstrated that hsCRP, IL-6, and D-dimer and ECG abnormalities were associated with CVD clinical outcomes among HIV-positive subjects.[1,2] Thus, the aforementioned findings and the results from the present study were consistent in showing that the biomarkers predict clinical CVD but not subclinical CVD, as measured by at rest ischemic ECG abnormalities. It is intriguing that the biomarkers were elevated among the 19 viral suppression participants who developed clinical CVD, irrespective of whether ischemic ECG abnormalities preceded the event, and that >50% of these asymptomatic participants experienced a serial ECG change before their CVD clinical outcome. This suggests that the CVD risk pathways might differ for the plasma biomarkers and ischemic ECG abnormalities studied. Early HIV autopsy studies found a high prevalence of histopathologic myocarditis.[13] More recent studies of healthy HIV participants have reported a high prevalence of functional and structural abnormalities on the echocardiogram.[14] Thus, it is possible that some of the ischemic ECG abnormalities we have reported reflect cardiac conditions other than ischemic heart disease.

Inflammatory markers have also been implicated in the development of ECG abnormalities unrelated to myocardial ischemia. In the Coronary Artery Risk Development in Young Adults study, the RR interval variability was inversely related to the hsCRP and IL-6 levels, suggestive of vagal signals modulating cytokine production.[15] In the Cardiovascular Health Study, CRP was associated with the presence of atrial fibrillation at baseline and predicted incident atrial fibrillation, consistent with inflammation-induced structural remodeling of the atria.[16] We could not assess the relation of atrial fibrillation with inflammation, because the prevalence was very low in the SMART study.[7]

The strengths of the present investigation were the prospective study design, the standard protocols used for 12-lead, at rest, ECG measurement, the central reading of the electrocardiograms, and the central determination of multiple plasma biomarker levels. Our study was subject to the limitations of using the Minnesota Code for ECG classification, which does not produce a clinical ECG interpretation, but rather classifies ECG abnormalities using rigid criteria.[17] However, this limitation can also viewed as a strength because using standardized criteria enabled comparison of the ECG findings among different studies and across visits from multiple clinical sites in the same study without the bias that could be introduced by subjective ECG interpretation. Finally, measurement of the biomarkers at a single point might not capture transient biomarker elevations and might lead to underestimation of the associations between biomarker levels and ischemic ECG changes.

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Table 1

Prevalent and incident ischemic electrocardiographic (ECG) abnormalities biomarker values

ECG Abnormality	DC and VS Participants (n =3,085)	hsCRP (μg/ml)	IL-6 (pg/ml)	D-dimer (μg/ml)
Prevalent abnormality				
Major abnormality	181 (5.9%)	2.13 (0.77–5.29)	1.68 (1.07–3.25)	0.22 (0.13–0.39)
Minor (but no major) abnormality	392 (12.7%)	2.16 (0.84–4.65)	1.81 (1.00–3.08)	0.20 (0.13–0.34)
Any abnormality (minor or major)	573 (18.6%)	2.16 (0.82–4.88)	1.77 (1.01–3.13)	0.20 (0.13–0.34)
No minor or major abnormality	2512 (81.4%)	1.59 (0.67–3.95)	1.57 (1.00–2.65)	0.18 (0.11–0.31)
Incident serial change (VS only)	VS participants (n = 1,411)			
Definite incident change	97 (6.9%)	2.45 (0.73–5.26)	1.84 (1.14–3.40)	0.25 (0.12–0.40)
Probable incident change	68 (4.8%)	2.08 (0.77–4.51)	1.81 (1.03–3.13)	0.22 (0.13–0.34)
Definite or probable change	165 (11.7%)	2.19 (0.75–4.99)	1.81 (1.10–3.29)	0.22 (0.12–0.38)
No definite or probable change	1246 (88.3%)	1.63 (0.68–3.94)	1.57 (0.97–2.67)	0.18 (0.11–0.31)

Data are presented as n (%) or median (interquartile range).

The numbers of Q- and ST-definite incident changes and corresponding percentage of participants with the change during follow-up were as follows: Q_1, 6 (0.4%); Q_2, 0 (0.0%); Q_3, 0 (0.0%); Q_4, 0 (0.0%); Q_5, 0 (0.0%); Q_6, 1 (0.1%); Q_7, 1 (0.1%); and Q_8, 1 (0.1%); and ST_1, 27 (1.8%); ST_2, 0 (0.0%); ST_3, 44 (2.8%); ST_4, 2 (0.1%); ST_6, 1 (0.1%); ST_7, 0 (0.0%); and ST_8, 24 (1.6%). Note, some patients had >1 definite incident ST change during follow-up.

DC = drug conservation; VS = viral suppression.

Table 2

Unadjusted and adjusted associations of high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and D-dimer with ischemic electrocardiographic (ECG) abnormalities

ECG Abnormality	Unadjusted		Adjusted	
	OR (95% CI)	p Value*	OR (95% CI)	p Value*
Prevalent ECG abnormalities				
Major abnormality				
hsCRP	1.39 (0.91–2.12)	0.10	1.13 (0.71–1.80)	0.69
IL-6	1.33 (0.88–2.00)	0.23	1.02 (0.64–1.63)	0.96
D-dimer	1.94 (1.26–3.00)	0.02	1.39 (0.87–2.23)	0.44
Any abnormality				
hsCRP	1.52 (1.17–1.96)	0.01	1.25 (0.95–1.65)	0.48
IL-6	1.31 (1.02–1.68)	0.02	0.95 (0.72–1.26)	0.99
D-dimer	1.54 (1.19–2.00)	0.007	1.13 (0.86–1.50)	0.61
Incident ECG serial change				
Definite change				
hsCRP	1.24 (0.70–2.19)	0.62	1.30 (0.68–2.45)	0.55
IL-6	1.47 (0.82–2.64)	0.53	1.44 (0.75–2.77)	0.66
D-dimer	1.48 (0.84–2.61)	0.18	1.19 (0.64–2.19)	0.51
Definite or probable change				
hsCRP	1.25 (0.61–1.60)	0.69	1.05 (0.63–1.74)	0.72
IL-6	1.45 (0.91–2.29)	0.28	1.11 (0.66–1.86)	0.95
D-dimer	1.53 (0.97–2.42)	0.09	1.21 (0.74–1.99)	0.42

Data presented compared greatest and lowest quartiles (cutoff for quartiles 1 and 4 were 0.69 μg/ml and 4.11 μg/ml for hsCRP, 1.00 pg/ml and 2.75 pg/ml for IL-6, and 0.11 μg/ml and 0.32 μg/ml for D-dimer, respectively).

Adjusted models controlled for age, gender, race, smoking status, body mass index, total/high-density lipoprotein cholesterol ratio, diabetes drug use, blood pressure-lowering drug use, lipid-lowering medication use, previous use of abacavir, previous use of a protease inhibitor, and hepatitis B and C co-infection.

CI = confidence interval.

*P values are for biomarker ORs from continuous models as a 1 SD increase on $\log_{10}$ scale.