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Regional coronary endothelial dysfunction is related to the degree of local epicardial fat in people with HIV

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Abstract

Background and aims: Coronary artery disease (CAD) is now an important cause of premature death in people with HIV but the causes of accelerated CAD are poorly understood. Epicardial adipose tissue (EAT) is metabolically-active and thought to contribute to CAD development. We tested the hypothesis that abnormal coronary endothelial function (CEF), an early marker and mediator of atherosclerosis, is related to the amount of local pericoronary EAT in HIV.

Methods: We studied 36 participants with HIV and no CAD (HIV+CAD–), 15 participants with HIV and known CAD (HIV+CAD+), and 14 age-matched, healthy participants without HIV (HIV–CAD–). To measure CEF, coronary MRI was performed before and during isometric handgrip exercise (IHE), an endothelial-dependent stressor. EAT was measured with MRI at the same imaging plane as CEF.

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Conceived and designed the experiments: AGH, RGW, GG, MS, MI. Software development: MS. Performed the experiments: AGH, MI, MS, SS, GB, RGW. Analyzed the data: AGH, MI, MS. Recruited participants: PB, TB, AH, RGW, GG. Contributed reagents/materials/analysis tools: MS. Wrote/edited the paper: MI, AGH, RGW, SS, MS, GB, TB, LM, SL, GG. All authors read and approved the final manuscript.

Conflict of interest:

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Results: CEF was significantly depressed, as measured by IHE-induced % coronary cross sectional area (CSA) change, in HIV+CAD- and HIV+CAD+ as compared to HIV-CAD- participants ($p<0.0001$). EAT thickness was significantly greater in HIV+CAD- and HIV+CAD+ participants as compared to HIV-CAD- participants ($p=0.001$). There was a significant inverse relationship between CEF and local EAT thickness and area ($R=-0.48$ and $R=-0.51$ respectively, $p<0.0001$ for both) among participants with HIV even after adjustment for cardiovascular risk factors. In participants with multiple CEF measures, CEF was lower in segments with higher EAT, other factors being equivalent.

Conclusions: There is a significant relationship between increased metabolically-active EAT and depressed local CEF in people with HIV, consistent with the hypothesis that increased epicardial fat contributes to accelerated CAD in persons with HIV.

Keywords

HIV; Epicardial fat; Coronary endothelial function

Introduction:

Survival has improved with antiretroviral therapies for people with HIV but accelerated coronary artery disease (CAD) is now an important cause of significant disability and premature mortality.¹ Although traditional cardiovascular risk factors are often present in individuals with HIV, these do not fully explain the elevated cardiovascular risk and are imperfect risk predictors in people living with HIV.^{2, 3} Moreover, the underlying mechanisms that predispose patients with HIV to accelerated atherosclerosis are poorly characterized and understood. HIV infected men compared to HIV uninfected men have greater amounts of epicardial adipose tissue (EAT),⁴ a form of metabolically-active visceral fat capable of releasing inflammatory adipokines hypothesized to contribute to CAD through local paracrine actions.⁴⁻⁶ In the general population, the degree of EAT is associated with increased coronary plaque burden and CV events.⁷⁻⁹ However, despite such prior observations that visceral adiposity is associated with increased cardiovascular risk in the general population,⁷⁻⁹ it is not known in people with HIV whether EAT causes coronary endothelial dysfunction, a mechanistic driver of CAD, and contributes to HIV-related atherosclerosis.

Abnormal endothelial function is both a contributor to, and marker of early coronary atherosclerosis. Abnormal coronary endothelial function (CEF) is mediated primarily by decreased nitric-oxide bioavailability and, as a result, plays a critical role in the development, progression and clinical manifestations of CAD.¹⁰ Depressed CEF is an independent predictor of cardiovascular events, and a potential target for medical interventions.¹¹⁻¹⁷ Although CEF was historically only assessed invasively in the catheterization laboratory by measuring changes in coronary arterial diameter and flow in response to endothelial-dependent vasomotor interventions, advances in magnetic resonance imaging (MRI) now allow for safe, non-invasive reproducible studies of CEF in the same individual over time and in low-risk populations.^{18, 19} We recently reported that CEF in individuals with HIV with no history or findings of heart disease is markedly impaired compared to that of age-matched individuals without HIV.²⁰ However, the mechanisms that

explain depressed CEF in persons with HIV are unknown. Likewise, MRI can quantify EAT and prior studies have shown that non-invasive measures of EAT are reproducible and have been studied in both populations with and without HIV.²¹ However, the relationship, if any, between EAT and a fundamental driver of CAD, namely depressed CEF, has never been studied in people with HIV but promises to provide important insights regarding potential pathophysiologic mechanisms of atherosclerosis in this population.

We therefore tested the hypotheses that EAT is increased in participants with HIV and that coronary endothelial dysfunction, an early marker of atherosclerosis and predictor of CAD events, is related to the amount of local pericoronary EAT adjacent to that coronary segment in participants with HIV. In addition, because CAD risk factors may differ among subjects and confound data interpretation, we also tested the hypothesis that in given participants with HIV with multiple CEF measurements, CEF is more depressed in coronary segments surrounded by greater EAT than in segments surrounded by less EAT, all other factors being equal.

MATERIALS AND METHODS

Participants:

The protocol was approved by the Johns Hopkins Medicine Institutional Review Board and complied with the Declaration of Helsinki. All participants provided written informed consent and were outpatients recruited at the Johns Hopkins Hospital with no known contraindications to MRI. Some of the patients included in this analysis were included in a previous study.²⁰ Three groups of stable, asymptomatic participants without diabetes were recruited from outpatient clinics at the Johns Hopkins Hospital: 1) participants with HIV with a zero coronary artery calcium score on recent (<2 years) computed tomography (HIV +CAD-) and no significant luminal stenosis (<30%) on prior computed tomography-angiography (performed in the majority of subjects (26/36;72%)); 2) participants with HIV with known CAD (HIV+CAD+) were those with documented CAD (without active symptoms of ischemia) on prior clinically-indicated coronary x-ray angiography or computed tomography angiography (stenosis of 30% to 70%) but no significant coronary luminal stenosis (defined as <50%) at or proximal to the segment imaged for CEF and 3) age-matched healthy control participants without HIV (HIV-CAD-) and with no history of CAD or traditional CAD risk factors, and for those over the age of 50 years with an Agatston coronary artery calcium score of zero on computed tomography. In the HIV+ groups, patients were receiving stable medical management. The HIV+ participants on antiretroviral therapy (ART) were on stable therapy for at least 1 year with a CD4 count >200 and undetectable viral load for the majority of the participants (Table 1).

Study protocol:

All subjects underwent MRI in the morning after fasting overnight (>8 hours) and prior to administration of any prescribed vasoactive medications. MR images were taken perpendicular to a proximal or mid well-visualized linear segment of the right coronary artery (RCA) that had not undergone prior intervention or had a significant stenosis (<20% stenosis by coronary angiogram). Baseline images were acquired at rest for cross-sectional

RCA area and velocity measurements, followed by repeat imaging at the same anatomic locations during 6–7 minutes of continuous isometric handgrip exercise (IHE) using an MRI-compatible handgrip dynamometer (Stoelting, Wood Dale, IL, USA) at 30% of maximum grip strength.^{18, 22} Heart rate and blood pressure were measured throughout the study and the rate pressure product (RPP) was calculated as previously^{18, 22} described. The main MRI endpoints were: change in IHE-induced cross sectional area (CSA) and coronary blood flow (CBF), and pericoronary EAT (referred to as “EAT” hereafter) around the RCA segment as detailed below.

In a subset of 15 participants with HIV, two segments were imaged for CEF and EAT in a straight portion of the mid RCA that did not include side branches. The RCA segments with a higher degree of EAT (based on EAT area and thickness) were placed in the “higher EAT” group and those with a lesser degree of EAT in the same vessel were placed in the “lower EAT” group. Measurements of local EAT and corresponding CEF were compared in two segments along the same vessel in a subset analysis according to group (lower EAT vs higher EAT).

MRI:

A commercial human 3.0 Tesla (T) whole-body MR scanner (Achieva, Philips, Best, NL) with a 32-element cardiac coil for signal reception was used. Cross-sectional anatomical and flow velocity encoded spiral MRI were obtained using single breath-hold cine sequences.¹⁸ Detailed MRI parameters for anatomical and velocity imaging were published previously.^{18, 22, 23} MRI for EAT was performed at the same imaging plane as CEF and used to measure local area and thickness in the atrioventricular groove. For EAT measures, spatial-spectral fat excitation was employed using an ECG triggered breath-hold cine sequence with 21 spiral interleaves and spatial resolution of $0.89 \times 0.89 \times 8 \text{ mm}^3$. The duration of the MRI exam was approximately 45–50 minutes.

Image analysis:

EAT (area and thickness in the AV groove surrounding the RCA) and coronary luminal cross-sectional area (rest and stress) were quantified using semi-automated software (Cine version 3.15.17, General Electric, Milwaukee, WI, USA) as previously described.^{19, 24} Coronary velocity was measured using commercially available software (QFLOW Version 3.0, Medis, Leiden, NL). A region of interest was traced using semi-automated software around a cross-section of the RCA to obtain peak diastolic coronary flow velocity (mean velocity of lumen pixels at peak flow) and coronary blood flow was calculated and converted to units of mL/minute using the adapted equation: $0.3 \times \text{cross-sectional area} \times \text{peak flow velocity}$.²⁵ Coronary segments with poor image quality (blurring due to artifact/patient motion) on either baseline or stress exams were excluded from analysis. Analysis of EAT and CEF was performed blinded to CAD and HIV status, and analysis of EAT was performed blinded to CEF results.

Statistics:

The data were tested for normality using the Shapiro-Wilk test. Parametric (Student's t-test and ANOVA) and non-parametric testing (Wilcoxon signed rank test for paired data and

Wilcoxon rank sum test for non-paired data) were used when appropriate for normally distributed and skewed data respectively, to compare the response to IHE from baseline for coronary area, velocity and flow measurements, and to compare CEF variables and fat quantification among groups. Results were presented as mean $\pm$ standard deviation (SD), unless otherwise indicated. We performed robust regression to assess the association between HIV status and both CEF variables and EAT measures. Since outliers can be masked and very hard to detect in multivariate or highly structured settings, and since conventional multiple linear regression models, based on ordinary least squares, could yield misleading results if the assumption of a normal distribution is not true, a 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 also performed to evaluate the relationship between the independent variables including EAT measures (EAT area and thickness) as well as clinical and demographic variables (sex, hypertension, hyperlipidemia and smoking), the dependent variables of CEF (% CSA and % CBF change with stress) and to assess whether CEF was independently associated with measures of EAT after adjustment for sex, hypertension, hyperlipidemia and smoking. Sensitivity analysis was performed to exclude the HIV+ subjects with detectable viral load to allow an analysis of a more homogenous population study. Statistical significance was defined as a two-tailed p -value 0.05.

Results

All participants completed the study and only 3 of 73 segments (4.1%) were excluded from analysis due to poor image quality (blurring of vessel during stress). Subject characteristics are reported in Table 1. The groups were well matched with no significant differences between the HIV– CAD– and HIV+CAD– groups with regard to age, BMI and conventional cardiac risk factors such as hypertension, dyslipidemia and smoking. Only 3 subjects in the HIV+CAD+ group had a history of a percutaneous coronary intervention (stents) and none had a history of coronary artery bypass surgery. Examples of typical MR images showing coronary artery cross-sectional area, velocity and fat in a study participant are shown Fig. 1.

Hemodynamic effects of IHE

Isometric handgrip exercise induced significant and similar mean hemodynamic changes in all groups. In the HIV+CAD– group, RPP at baseline was 9536 ± 2226 mmHg*bpm and increased to 11151 ± 2532 mmHg*bpm with IHE (17% from baseline, $p < 0.0001$) while in the HIV+CAD+ group, RPP increased from 10675 ± 2433 mmHg*bpm to 12793 ± 2616 mmHg*bpm with IHE a 21% increase from baseline, $p < 0.0001$). The RPP in the HIV–CAD– increased from 8725 ± 1872 increased to 10816 ± 2364 mmHg*bpm, (25% increase from baseline, $p < 0.001$). There were no significant differences in the RPP % change with IHE from baseline among the three groups.

Coronary Vasoreactivity: coronary cross sectional area change with stress

There was no significant difference in the baseline CSA among the three groups. The mean IHE-induced percent change in stress-induced CSA was significantly higher in the HIV–CAD– participants ($10.1 \pm 5.5\%$) than in those with HIV+CAD– ($0.2 \pm 12.3\%$, $p < 0.001$ vs. HIV–CAD–) and those with HIV+CAD+ ($-1.1 \pm 3.8\%$, $p < 0.0001$ vs. HIV–CAD–, Fig 2A). The impaired CSA response of HIV+CAD– participants was not significantly different from that of the HIV+CAD+ participants (Fig.2; panel A). Similar results were achieved when a sensitivity analysis was performed excluding the HIV+ subjects with detectable viral load (4 subjects from the HIV+CAD– group and 3 subjects from the HIV+CAD+ group). In addition, using regression analysis, HIV status was independently associated with worse %CSA change ($P = 0.005$) after adjusting for sex and cardiac risk factors.

Coronary blood-flow change with stress

There were no significant differences in baseline coronary blood flow among the three groups. The mean percentage change in coronary blood-flow with IHE stress was significantly greater in the healthy HIV–CAD– group ($33.2 \pm 15.2\%$) than in the HIV+CAD– group ($0.2 \pm 22.5\%$, $p < 0.0001$ vs. HIV–CAD–) and in the HIV+CAD+ group ($2.3 \pm 17.5\%$ vs. Healthy, $p < 0.0001$ Fig 2B). Similar results were obtained when a sensitivity analysis was performed excluding the HIV+ subjects with a detectable viral load. Using regression analysis, HIV status was independently associated with worse %CBF change ($p < 0.001$) after adjusting for sex and cardiac risk factors.

Local epicardial adipose tissue: EAT quantification

The mean distance from the RCA ostium to where the EAT and CEF measurements were made was 6.7 ± 2.5 cm. Mean EAT thickness and area were significantly greater in the HIV+CAD– group (EAT thickness 16.3 ± 6 mm and EAT area 265.7 ± 129.7 mm²) compared to that in healthy HIV–CAD– subjects (10.7 ± 3.3 mm and 184.6 ± 100 mm², $p = 0.0004$ and $p = 0.03$, respectively, Fig 2C). Similarly, EAT thickness and area were greater in the HIV+CAD+ group (13.9 ± 3.1 mm and 259.8 ± 85.7 mm²) compared to healthy HIV–CAD– subjects (10.7 ± 3.3 mm and 184.6 ± 100 mm², $p = 0.001$ and $p = 0.02$ respectively, Fig 2D). Similar results in terms of differences in EAT between groups were attained when a sensitivity analysis was performed excluding the HIV+ subjects with detectable viral load. Using regression analysis, HIV status was independently associated with both increased EAT thickness and area ($p < 0.001$ for each) after adjusting for sex and risk factors.

Relationship between endothelial-dependent coronary vasoreactivity and local EAT

In the subjects with HIV ($N = 51$), there was a significant inverse relationship between the degree of local EAT and the %CSA change with IHE stress in that coronary segment (EAT thickness: $r = -0.48$, $p < 0.0001$; EAT area: $r = -0.51$, $p < 0.0001$; Fig. 3). The relationship between the dependent variable of CEF (%CSA change with stress) and the independent variables of EAT measures (EAT thickness and area) were statistically significant even after adjusting for sex and CV risk factors (such as hypertension, smoking and hyperlipidemia) in HIV+ individuals but not in HIV– individuals. In the HIV+ individuals, there was no correlation between CEF parameters (%CSA and %CBF change with IHE) and duration of

antiretroviral therapy (Fig 4). In the participants without HIV (N=14), there was no significant relationship between EAT and percent CSA change with handgrip stress ($r=0.12$, $p=0.6$; data not shown). No significant relationship was observed between local EAT thickness and percent coronary flow change with stress in participants with HIV (flow change vs. EAT thickness: $r=-0.12$, $p=0.4$; vs. EAT area: $r=-0.14$, $p=0.3$). Thus, EAT correlates with local area changes (CSA) in participants with HIV but not with blood flow changes that can be influenced by non-local, “downstream” factors.

In a subset of 15 participants with HIV, two segments of the mid RCA per subject were imaged. There was no systematic bias in EAT distribution between proximal and distal segments in these subjects and no significant difference in EAT measures between more proximally located and distal segments. Importantly, in paired comparison, the segments with a higher degree of EAT (mean=304±136 mm²) had significantly worse CEF (mean % CSA change with stress: -4.3±8.7%) than the segments with a lesser degree of EAT (mean EAT area=229±95 mm²; % CSA change: +3.9±6.4%, $p=0.01$ vs. higher EAT segments, Fig. 5) from the same individual, all other risk factors being equivalent.

Discussion

We previously reported that coronary endothelial function was reduced in patients with known CAD and those with HIV even in the absence of CAD as compared to that of non HIV age-matched individuals^{18, 20, 22}. This study demonstrates that abnormal coronary endothelial function and local EAT can be detected during a single, noninvasive 3-T MRI examination, that EAT is increased in participants with HIV, and importantly, that abnormal coronary endothelial dependent vasoreactivity is inversely related to the degree of local EAT in the same coronary segment among participants with HIV. In addition, this study demonstrates by paired-analysis of multiple CEF measures in a given participant with HIV, that coronary segments with increased EAT have worse CEF than segments with less EAT, all conventional systemic CAD risk factors equivalent in those two coronary segments. Although conventional CAD risk factors contribute to atherosclerosis and impair CEF in individuals with HIV, this work demonstrates that increased EAT in individuals with HIV is closely associated, anatomically, with impaired local CEF, a driver of coronary atherosclerosis.

The CEF values reported here are similar to those previously reported using MRI^{18, 19, 22} and invasive techniques.^{15, 27, 28} Furthermore, we previously reported that the normal vasodilatory response to IHE is completely abolished after administering an NO-synthase inhibitor. Thus the coronary artery vasoreactive response to IHE primarily reflects NO-mediated coronary endothelial function.²² The ability to measure both EAT and endothelial-dependent coronary vasoreactivity in a single noninvasive examination enables a more complete measure of early atherosclerotic disease and potential contributing factors to CAD pathogenesis in persons with HIV. Moreover, the non-invasive imaging protocol makes it feasible to perform studies in low-risk populations, repeat them over time, and assess both the degree of EAT and the coronary vascular response to potential therapeutic interventions. Finally, although our study detected a relationship between endothelial-dependent coronary vasodilation (area change) and EAT, there was no relationship between coronary flow

change with IHE stress in participants with HIV. These findings suggest that early *local* functional atherosclerotic changes (e.g., coronary cross-sectional area) are more closely related to *local* EAT surrounding the coronaries than to endothelial function measures that incorporate distal and nonlocal downstream parameters including those of the microcirculation (e.g., coronary blood flow).

EAT is a metabolically active form of visceral fat that is increased in people with HIV, may contribute to the inflammatory milieu, and correlates with an increased risk of atherosclerosis.^{29,30} Coronary arteries that run below a myocardial bridge and not surrounded by EAT, are typically spared from atherosclerosis and thought not to be surrounded by fat (although the latter was recently questioned.³¹ The degree of EAT measured in the current study is similar to that observed in prior CT and MRI studies^{24, 32, 33} and confirms prior findings that EAT is increased in participants with HIV taking ART.^{34, 35} Furthermore, similar to visceral fat in other depots, EAT exhibits increased expression of proinflammatory cytokines in patients with CAD at the time of coronary artery bypass surgery.^{36, 37} Moreover, EAT contains higher levels of inflammatory cytokines (such as IL-6) than does subcutaneous fat in the same individual.⁶ The evidence that EAT may contribute to atherosclerosis, possibly mediated by local paracrine effects and inflammation, was recently reviewed.³⁸ The observation here in participants with HIV that visceral fat in the form of EAT and the vascular dysfunction of early atherosclerosis not only coexist in coronary arteries, but are also closely related is novel and consistent with a mechanistic relationship. In addition, we observed varying degrees of EAT within a single coronary artery and a relationship between higher EAT and depressed CEF within the same individual not confounded by conventional systemic cardiovascular risk factors. In contrast to the findings in participants with HIV, healthy HIV–CAD– subjects had normal CEF and no relationship between coronary endothelial function and local EAT. This is likely due to the relatively narrow and normal range of CEF values and lower EAT in HIV–CAD– subjects in this modest population. Inclusion of persons without HIV, but with CAD risk factors or CAD itself in future studies would be required to more carefully address the different question of the role of EAT in populations without HIV.

Several previous studies evaluated the relationship between brachial artery endothelial function (flow-mediated dilation) and EAT in populations without HIV and reported varying results.^{39, 40} Although some studies found a relationship between increased EAT and depressed peripheral endothelial function,^{39, 41} others found no significant correlation between the two parameters.⁴⁰ The latter findings may be explained by the lack of proximity between EAT and systemic vessels. Moreover, although atherosclerosis is a systemic process, studies of different vascular territories have shown that vasoreactivity is not always uniform across vascular regions within^{23, 42} the same individual. Other data suggest that peripheral and coronary endothelial function measures may not be strongly related^{23, 42, 43} possibly due to differences in vascular properties. Furthermore, acute brachial arterial plaque rupture rarely occurs in contrast to acute coronary plaque rupture. Thus, the non-invasive measurement of CEF is likely more relevant than measures of systemic endothelial function for defining factors related to local coronary artery atherosclerosis and plaque progression in people living with HIV.

Limitations

One limitation of the current MRI approach is the inability to detect inflammation directly in surrounding fat tissue, and the inability to identify different types of fat (i.e. metabolically inactive vs. active adipose tissue). However, in the future, this may be possible with the implementation of proton spectroscopy or in conjunction with PET imaging. For this study, we limited our evaluation of coronary segments to the RCA only because EAT can differ among coronary distributions and we wanted to minimize potential confounding. In addition, image quality for the coronaries is typically better in the RCA due to its proximity to the surface coil with improved signal. Future technical developments designed to improve spatial resolution of the left anterior descending artery and the left circumflex artery (greater distance from cardiac coil) and volumetric coverage will likely advance endothelial function imaging and EAT studies. In addition, there are inherent limitations to the case control study design which allow us to infer only an association and not causality. Future mechanistic studies which manipulate EAT stores are needed to test whether increased EAT per se causes endothelial dysfunction. Although multidetector computed tomography (CT) has been used to assess EAT and coronary plaque in patients with HIV,³⁴ the exposure to ionizing radiation and contrast media often limits repeated studies and stress studies (such as IHE) as well as applications in low-risk populations. CT is also unable to measure coronary velocity or flow as done here. MRI studies of the coronaries and EAT may be safely performed in low-risk populations and repeated studies over time and do not require contrast (gadolinium), which offers the ability to safely study patients with renal insufficiency. In addition, although IHE can induce diastolic dysfunction and impair myocardial metabolism in patients with critical coronary artery disease, it is unlikely that either factor played a systematic role in influencing the regional differences in coronary endothelial dysfunction observed or the relationship of CEF to EAT since most subjects had no coronary disease and those that did (HIV+CAD+ participants) did not have critical disease in the coronary region studied. Finally, there was a difference in age between the HIV-/CAD- and HIV+/CAD+ groups that may explain some of the difference in CEF between those two groups. However, there was no significant difference in age between HIV-/CAD- and HIV+/CAD-, our main comparison group, that could account for between group differences in CEF or EAT.

Conclusion

In summary, the present findings demonstrate that EAT is increased and local coronary endothelial function depressed in participants with HIV. Importantly, we observed that locally depressed CEF is closely and independently correlated with increased EAT in participants with HIV, as a group and within subjects by paired analysis. These findings indicate that abnormal local endothelial function in a coronary segment is associated with EAT adjacent to that coronary artery segment and therefore that EAT and physiological indicators of coronary vascular pathology are related in patients and can be detected noninvasively in humans. These observations support future trials to determine whether strategies to reduce metabolically active increased EAT in populations with HIV improves coronary endothelial dysfunction and limits accelerated CAD progression and events.

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Fig 1: MR anatomical, EAT (epicardial adipose tissue) and flow velocity images of right coronary artery.

(A) Scout scan obtained parallel to the right coronary artery (RCA) in an adult person with HIV is shown together with the location for cross sectional imaging of the coronary (yellow line). (B) Cross-sectional image from the same subject perpendicular to the RCA (red box) from which area measurements are made. (C) Cross sectional flow velocity image of the RCA in the same segment (red box). (D) Fat excited image showing fat surrounding the same cross sectional RCA segment (local epicardial adipose tissue).

Fig 2: Subjects with HIV have endothelial dysfunction and an increased amount of epicardial adipose tissue compared to subjects without HIV.

(A and B) Relative changes (% change) in coronary artery area (CSA) and peak coronary blood flow (CBF) during isometric handgrip exercise (IHE) are shown for HIV-CAD- (striped bars), HIV+CAD- (black bars), and HIV+CAD+ groups (gray bars). * $p < 0.001$ vs. HIV-CAD- response. ** $p < 0.0001$ vs. HIV-CAD- response and # $p < 0.05$ vs. HIV-CAD- response. (C and D) Summary results are shown for mean EAT, both thickness and area, in the same three groups. The degree of EAT thickness and area in patients with HIV is significantly higher than in the non HIV participants * $p < 0.001$ vs. HIV-CAD- and # $p < 0.05$ vs. HIV-CAD-, respectively). Error bars represent SD.

Fig 3: Vasoreactive response to endothelial dependent stressor isometric handgrip exercise is inversely related to the degree of epicardial adipose tissue in HIV+ subjects.

Individual data points showing MRI measures of % CSA (coronary cross sectional area) change with IHE (isometric handgrip exercise) *versus* local EAT (epicardial adipose tissue) thickness (A) and EAT area (B) in people with HIV (N= 66 segments in 51 subjects). There is a significant inverse relationship between %CSA change and the degree of EAT using both measures.

Fig 4: The relationship between coronary endothelial function and the duration of antiretroviral therapy in HIV+ participants.

Individual data points are presented showing MRI measures of % CSA (coronary cross sectional area) change with isometric handgrip exercise (IHE) *versus* duration of ART (antiretroviral therapy), and % CBF (coronary blood flow) change *vs.* duration of ART in years.

Fig 5: Coronary vasoreactivity is worse in segments with increased epicardial adipose tissue area.

CSA (coronary cross sectional area) change with IHE (isometric handgrip exercise) in segments with lower EAT (epicardial adipose tissue, black bar) and in those segments with higher EAT area (striped bar) in 15 subjects with HIV (2 segments per individual). The % CSA change with IHE stress was reduced in higher EAT segments compared to % CSA change in paired lower EAT segments within a given individual. * $p=0.01$. Error bars represent SD.

Table 1.

Table values are expressed in mean $\pm$ SD for continuous variables and n (%) for categorical variables.

Characteristics	HIV-/CAD- (n=14)	HIV+/CAD- (n=36)	HIV+/CAD+ (n=15)	<i>p</i> value (HIV- CAD- vs. HIV +/CAD-)	<i>p</i> value (HIV +/CAD- vs. HIV+/CAD+)
Age (years)	50 $\pm$ 7	53 $\pm$ 8	57 $\pm$ 4	0.2	0.07
Male gender	5 (36)	24 (66)	11 (73)	0.05	0.6
BMI (kg/m ²)	25 $\pm$ 3	27 $\pm$ 4	26 $\pm$ 8	0.1	0.6
Waist circumference (inches)	N/A	37.6 $\pm$ 6	36.9 $\pm$ 7	-	0.9
Waist to hip ratio	N/A	0.99 $\pm$ 0.3	1.0 $\pm$ 0.3	-	0.95
HTN	2 (14)	10 (28)	8 (53)	0.3	0.08
Smoker	0	1 (2)	6 (40)	0.34	<0.05
Hyperlipidemia	1 (7)	8 (22)	7 (46)	0.2	<0.05
Statin	1 (7)	8 (22)	7 (46)	0.2	<0.05
LDL-c (mg/dL)	120 $\pm$ 70	91 $\pm$ 42	91 $\pm$ 27	0.08	0.9
HDL-c (mg/dL)	55 $\pm$ 40	60 $\pm$ 30	53 $\pm$ 19	0.6	0.4
Triglyceride (mg/dL)	88 $\pm$ 50	114 $\pm$ 54	129 $\pm$ 58	0.1	0.4
CD4 count (mm ³)	N/A	611 $\pm$ 480	619 $\pm$ 254	-	-
HIV RNA, <20 copies/mL	N/A	32 (89)	12 (80)	-	-
ART	N/A	34 (94)	11 (73)	-	-
Treatment with protease inhibitors	N/A	6 (16)	6 (40)	-	0.12

N/A=not available, ART=anti retroviral therapy, BMI=body mass index, CABG=coronary artery bypass graft surgery, CAD=coronary artery disease, HLD=hyperlipidemia, HDL=high density lipoprotein, LDL-C=low density lipoprotein cholesterol, NS=non-significant, PCI=percutaneous coronary intervention; SD=standard deviation.