Abstract #744

Pericardial Fat Density:
A Novel Marker of Cardiometabolic Risk in HIV Infection

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BACKGROUND

Pericardial fat volume is associated with inflammation, insulin resistance, and vascular disease in HIV-infected patients on antiretroviral therapy (ART). Visceral abdominal fat volume AND density are associated with metabolic syndrome components in the general population. The relationship between pericardial fat density, inflammation, and cardiometabolic risk in the HIV-infected population is unknown.

The objective of this study was to explore whether pericardial fat volume and density were associated with insulin resistance independent of each other and biomarkers of inflammation and immune activation in treated HIV infection.

METHODS

Design: Cross-sectional

Subjects:

•**S**topping **A**therosclerosis and **T**reating **U**nhealthy bone with **R**osuvastati**N** in HIV (SATURN-HIV) is a randomized, placebo-controlled trial of 10mg daily rosuvastatin. This is a cross-sectional analysis of baseline data.
•All were ≥18 years of age, on stable ART with LDL-cholesterol (LDL-C) ≤130mg/dL and had either heightened T-cell activation (CD8+CD38+HLA-DR+ ≥19%) or increased inflammation (high sensitivity C-reactive protein (hsCRP ≥2mg/L) at baseline.

Pericardial Fat

•All subjects underwent 64-slice multidetector non-contrast CT scan of the chest. Three-millimeter slices were obtained from the carina to the diaphragm with prospective ECG gating at 60% of the R-R interval. All measurements were made offline by a single reader (CTL) using Aquarius iNtuition Cloud software (Terarecon, San Mateo, CA USA).
•**Volume:** Using a semi-automatic segmentation technique developed by the Framingham Heart Study, pericardial fat was defined as all fat tissue (-195 to -45 Hounsfield Units) within the pericardial sac.
•**Density:** Pericardial fat density (mean attenuation in Hounsfield Units) was measured in 3 consecutive slices through the center of the heart (see Figure). The average of the 3 measurements was used for analyses.

Inflammation and Immune Activation:

•CD4+ and CD8+ T-cell activation (CD38 and HLA-DR co-expression)
•Inflammatory (CD14+CD16+) and patrolling ($CD14^{dim}CD16+$) monocytes.
•Plasma markers of monocyte activation: Soluble CD163 and CD14
•Plasma biomarkers of inflammation, coagulation, and endothelial activation (Interleukin-6, tumor necrosis factor-α receptors I/II, soluble intracellular and vascular cell adhesion molecules, d-dimer, fibrinogen)

Statistics:

•Spearman correlations
•Multivariable linear regression model of the relationship between pericardial fat and insulin resistance (logHOMA-IR): Candidate variables were demographics, traditional cardiovascular risk factors, HIV disease factors, measures of total body and regional adiposity, and biomarkers of systemic inflammation and immune activation. Variables were selected by forward and backward selection, with a significance level of p<0.15 for inclusion in the model. Pericardial fat volume was forced into the final model.

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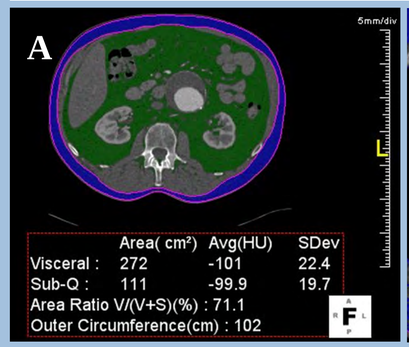
RESULTS

Table 1: Baseline characteristics of study subjects from the SATURN-HIV trial.

	Overall (n = 147)
Demographics	
Age (years)	**46 (40-53)**
Male	**115 (78%)**
African American	**101 (69%)**
HIV Parameters	
Current CD4+ count (cells/μl)	**613 (425-853)**
Nadir CD4+ count (cells/μl)	**179 (86-298)**
HIV duration (years)	**12 (6.2-18)**
Antiretroviral Therapy duration (years)	**5.3 (3.2-9.8)**
Protease Inhibitor duration (years)	**3.5 (0.7-7.1)**
Undetectable viral load (<48copies/ml)	**104 (70%)**
Traditional Cardiovascular Risk Factors	
Systolic Blood Pressure (mmHg)	**121 (112-132)**
HDL Cholesterol (mg/dL)	**46 (37-57)**
LDL Cholesterol (mg/dL)	**97 (77-113)**
Non-HDL Cholesterol (mg/dL)	**123 (102-144)**
Homeostasis Model Assessment of Insulin Resistance (HOMA-IR)	**1.8 (1.1-3.3)**
Metabolic Syndrome	**114 (22%)**
Current smoker	**93 (63%)**
Family History of Myocardial Infarction	**46 (31%)**
10-year Framingham risk score (%)	**3.0 (1.0-7.0)**
Reynold's Risk Score (%)	**2.1 (0.9-5.1)**
Body Fat Composition	
Body Mass Index (kg/m²)	**27 (23-30)**
Total Limb Fat (kg)	**8.8 (4.9-14)**
Total Trunk Fat (kg)	**13 (7.7-18)**
Pericardial Fat (cm³)	**68 (47-92)**
Pericardial Fat Density (HU)	**-86.8 (-88.7, -85.0)**
Current Medication Use	
Anti-hypertensive medication use	**36 (24%)**
Fibrate use	**4 (3%)**
Fish oil use	**12 (8%)**
Current PI use	**72 (49%)**
Current AZT or D4T use	**8 (5%)**
Current abacavir use	**7 (5%)**

Figure: Fat density (mean attenuation in Hounsfield Units) can be measured in the abdomen using semi-automatic edge detection software as shown in A. For this study, this tool was adapted to the pericardial fat depot by retracing the visceral fat border to the pericardial border as shown in B. The average of 3 measurements through the center of the heart was used for analysis.



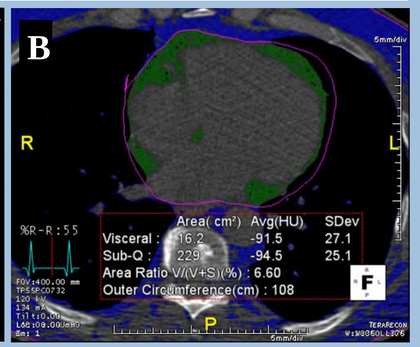


Table 2: **In contrast to volume, pericardial fat density did not correlate with measures of regional or total body adiposity, but did correlate with waist-hip ratio. * p > 0.1**

	PCF Density		PCF Volume	
	Spearman r	p-value	Spearman r	p-value
Current CD4+ count (cells/μl)	*	*	*	*
Nadir CD4+ count (cells/μl)	*	*	-0.200	0.016
ART duration (years)	-0.206	0.017	*	*
PI duration (years)	-0.227	0.014	*	*
Systolic Blood Pressure (mmHg)	*	*	*	*
Anti-hypertensive medication use	*	*	0.224	0.007
HDL Cholesterol (mg/dL)	0.163	0.049	-0.330	<0.001
LDL Cholesterol (mg/dL)	-0.175	0.035	*	*
Metabolic Syndrome	*	*	-0.364	<0.001
Body Mass Index (kg/m²)	*	*	0.512	<0.001
Waist-to-hip ratio	-0.337	<0.001	0.597	<0.001
Total Limb Adipose Tissue (kg)	*	*	0.417	<0.001
Total Trunk Adipose Tissue (kg)	*	*	0.603	<0.001

Table 3: **Pericardial fat density was associated with insulin resistance (logHOMA-IR) independent of pericardial fat volume and soluble markers of immune activation.** Parameter estimates are expressed per standard deviation increase for continuous variables or yes vs. no for dichotomous variables. HOMA-IR, Homeostatic model assessment of insulin resistance; HU, Hounsfield Units; HDL, high-density lipoprotein; BMI, body mass index. * = Non-normally distributed variables were log-transformed prior to analyses. Model R2 = 0.4383. **p <0.05 in red**

	β	P value
Pericardial fat density (HU)	-0.150	**0.024**
Pericardial fat volume (ml)*	0.096	0.232
Non-HDL (mg/dl)	0.063	0.296
Metabolic syndrome (yes vs. no)	0.658	**<0.0001**
BMI (kg/m²)	0.186	**0.017**
Soluble CD163 (ng/ml)*	0.142	**0.019**
Soluble CD14 (ng/ml)*	-0.097	0.108
Current Smoker (yes vs. no)	-0.282	**0.023**

CONCLUSIONS

•***Lower*** pericardial fat density—a simple measure obtained from non-contrast cardiac CT—is a novel marker of insulin resistance that is independent of pericardial fat volume and measures of total body adiposity.
•Future studies should examine the utility of combining volume and density to develop a pericardial fat score—akin to the Agatston score for coronary artery calcium—for populations at risk of metabolic complications of statin therapy such as HIV-infected patients on ART.