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Quantification of epicardial fat using non contrast cardiac CT in an HIV population: Reproducibility and association with other body fat indices

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HIGHLIGHTS

- Assessment of epicardial fat volume is highly reproducible.
- Epicardial fat volume and epicardial fat area have a good correlation to BMI.
- Epicardial fat volume correlates best with DEXA-derived total body fat and trunk fat.
- Epicardial fat volume should be considered over other CT assessment methods when quantifying epicardial fat in HIV patients.

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ABSTRACT

Purpose: To assess the reproducibility of different epicardial fat measurement and their association with other adiposity measurements in HIV-infected and non-HIV-infected patients.

Methods and materials: In this cross-sectional study, 167 HIV-infected and 58 non-HIV-infected consecutive participants (200 males; mean age 56 years) with low/intermediate cardiovascular risk were recruited between 2012 and 2017 from a large prospective cohort and underwent non-contrast cardiac CT. Two independent observers measured epicardial fat volume, area and thickness in all participants. For intra-observer agreement, one observer did a second assessment in a subset of 40 patients. Agreement was assessed with the intraclass correlation coefficient (ICC). Pearson's correlation was estimated to assess the association between epicardial fat, body-mass index (BMI) and dual-energy x-ray absorptiometry (DEXA) derived percentage of body fat.

Results: Inter-observer agreement was excellent for epicardial fat volume (ICC 0.75) and area (ICC 0.95) and good for epicardial fat thickness (ICC near the left anterior descending artery (LAD) 0.64, ICC near right coronary artery (RCA) 0.64). Intra-observer agreement was excellent for epicardial fat volume (ICC 0.97), area (ICC 0.99), thickness at LAD (ICC 0.71) and good for epicardial fat thickness at RCA (ICC 0.68). Epicardial fat volume had a better correlation to total body fat ($r = 0.28$, $p < 0.001$) and trunk fat ($r = 0.37$, $p < 0.001$), in comparison to other epicardial fat indices.

Conclusion: Assessment of epicardial fat volume is highly reproducible in both HIV-infected and non-HIV-infected patients and shows a superior correlation with DEXA-based body and trunk fat measurements. Epicardial fat volume should be considered over other CT assessment methods when quantifying epicardial fat in HIV patients.

Abbreviations: CT, computed tomography; DEXA, dual-energy x-ray absorptiometry; ICC, intraclass correlation coefficient; BMI, body-mass index; LAD, left anterior descending artery; RCA, right coronary artery; HU, Hounsfield units; IQR, interquartile range; HIV, Human immunodeficiency virus.

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1. Introduction

Epicardial fat is a visceral fat depot surrounding the heart, between the myocardium and the visceral pericardium. It predominates in the atrio-ventricular and interventricular grooves, in direct vicinity to the coronary arteries [1,2]. More than an inert lipid compartment, epicardial fat is a regional adipose tissue depot that secretes hormones and inflammatory adipokines, some of which with an alleged role in the pathogenesis of coronary atherosclerosis [3–5].

Studies have shown an association between epicardial fat and the presence and progression of coronary artery disease as defined by coronary artery computed calcium score, presence and extent of various types of coronary plaque, as well as cardiovascular events including myocardial infarction, revascularization or death [6–9].

In recent years, there has been an increased interest in the assessment of epicardial fat in the HIV population. People living with HIV are known to have a greater risk of coronary artery disease than non-infected individuals [10,11], although the mechanisms underlying this increased risk are not yet fully understood. HIV infection is also accompanied by changes in body fat distribution [12] and these may play an active role in promoting atherosclerosis. Evaluating epicardial fat may help understand the interaction between adipose tissue and HIV-specific factors, as well as its involvement in the pathogenesis of coronary artery disease. Accurate validation of quantitative tools used in the assessment of epicardial fat is therefore pivotal.

The purpose of this cross-sectional study was to compare the reproducibility of different epicardial fat measurement methods using non-contrast cardiac computed tomography (CT) and to evaluate their association with other adiposity measurement including body-mass index (BMI) and dual-energy x-ray absorptiometry (DEXA)-derived percentages of body fat in order to determine which epicardial fat measurement parameter correlates best to other well validated fat indices and accurately reflects epicardial fat amount. The study was conducted in HIV-infected and non-HIV-infected participants from the Canadian HIV and Aging Cohort Study (CHACS) [13], a large multicenter prospective cohort following both HIV and non-HIV individuals.

2. Methods

2.1. Study design and population

This is a cross-sectional study, nested in the CHACS. CHACS is an ongoing multicenter, prospective, controlled cohort, actively following more than 1100 HIV-infected and non-HIV-infected participants in 10 Canadian centers. HIV-infected participants aged 40 years old or older, or who have lived with HIV for 15 years or more, were recruited between 2012 and 2017 from the HIV clinics of the participating centers. Non-HIV-infected individuals were selected from the general population reached through HIV participating clinics, HIV prevention clinics, general internal medicine clinics and participating community members. The non-HIV-infected participants recruitment was guided by attempting to obtain a frequency-match for age, sex and smoking status. Approval was obtained from the institutional review board of the CHACS and participating centers and all participants gave written informed consent.

In the present study, a total of 225 consecutive participants (mean age 56.0 ± 7.4 [standard deviation], 200 men; mean age, 55.4 ± 7.0 years; 25 women; mean age, 61.4 ± 8.3 years), from the CHACS cohort with a low to intermediate cardiovascular risk (10-year Framingham risk score 5–20 %) and without symptoms or history of coronary artery disease were prospectively recruited to undergo cardiac CT. All participants were also invited to undergo whole body DEXA to assess epicardial and total body fat content.

2.2. Non-contrast cardiac CT and whole body DEXA acquisition

256-slice CT scanner (Brilliance iCT, Philips Healthcare, Best, The Netherlands) was used to perform non-contrast cardiac CT. The following parameters were used: slice thickness 2.5 mm (mean increment 1.5 mm), matrix 512 × 512, field-of-view 250 mm, scan voltage 120 kV, gantry rotation 270 ms and prospective electrocardiographic (ECG)-gating. All images were reconstructed using a hybrid iterative reconstruction algorithm (Philips iDose, Philips Healthcare, level 3). Effective CT radiation dose was calculated by multiplying dose-length product with a conversion coefficient for the chest (k = 0.014 mSv·cm/mGy). Dose-length product was 124 [116.2–135.9] mGy x cm and effective radiation dose was 1.70 [1.58–4.25] mSv.

Whole body DEXA scanning was performed using a Lunar Prodigy (GE Healthcare, Madison, WI). Total body fat and lean mass were measured, as well as regional fat content and lean mass of the trunk and lower limbs.

2.3. Epicardial fat quantification

Epicardial fat analysis was done using axial CT slices, with a semi-automated software (Aquarius iNtuition 4.4.6, TeraRecon Inc, Foster City, CA, USA). Epicardial fat was defined as the adipose tissue between the surface of the myocardium and the visceral pericardium.

2.3.1. Epicardial fat volume

Epicardial fat volume (cm^3) was segmented by tracing manually the pericardium every two to three axial slices from the pulmonary artery bifurcation to the apex of the heart (Fig. 1). CT attenuation thresholds between -190 and -30 Hounsfield units (HU) were used to select the epicardial fat and exclude any other tissue from volume quantification [14,15]. The epicardial fat volumes measured at each level were then summed to obtain the total epicardial fat volume taking into account the intersection gap.

2.3.2. Epicardial fat area

Epicardial fat area was measured by manually tracing a single region of interest along the pericardium which selected the heart and epicardial fat. Then, we selected the same HU range as described for epicardial fat volume quantification to include epicardial fat and exclude the heart from area quantification. The semi-automated software calculated then the area of epicardial fat. This was done at the level of the middle third of the right coronary artery (RCA) (Fig. 2).

2.3.3. Epicardial fat thickness

Epicardial fat thickness was measured on a single axial slice at two different locations: the atrioventricular groove at the level of the middle third of the RCA and next to the left anterior descending coronary artery (LAD). Maximal thickness was measured from the myocardium to the visceral pericardium, perpendicular to the surface of the heart (Fig. 2).

2.3.4. Pericoronary artery fat volume

Pericoronary fat volume was measured along the middle segment of the RCA in the atrioventricular groove using the same HU range as described above. A circle with a radius of 5 mm was drawn around the coronary artery, starting at the same level as epicardial fat thickness measurement (Fig. 3). We repeated the measurement in 6 consecutives axial images. Since the slice thickness was 2.5 mm, with mean increment 1.5 mm, this resulted in a cylinder of approximately 9 mm length and a diameter of 10 mm. This was done in each participant of the study.

2.4. Inter-and intra-observer agreement

For inter-observer agreement assessment, two observers performed the measurements of epicardial fat volume, area and thickness, as well as pericoronary volume in all participants, independently of each other.

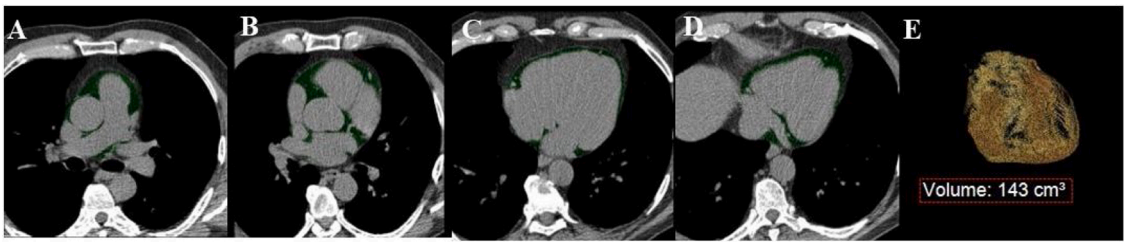

Fig. 1. Epicardial fat volume measurement.
Epicardial fat volume was segmented by manually tracing the pericardium on axial slices from the pulmonary artery bifurcation to the apex of the heart (A, B, C and D). CT attenuation thresholds between -190 and -30 Hounsfield units were used. Data were then summed to obtain the total epicardial fat volume (E).

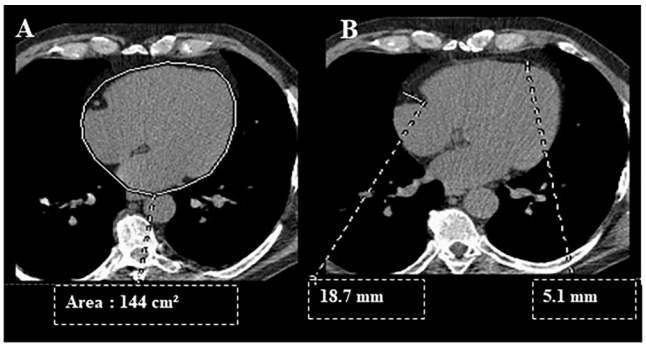

Fig. 2. Epicardial fat area (A) and thickness (B) measurement.
Epicardial fat area was measured at the level of the middle third of the right coronary artery (RCA). Epicardial fat thickness was measured on a single axial slice at two different locations: the atrioventricular groove at the level of the middle third of the RCA and next to the left anterior descending coronary artery (LAD). Maximal thickness was measured from the myocardium to the visceral pericardium, perpendicular to the surface of the heart.

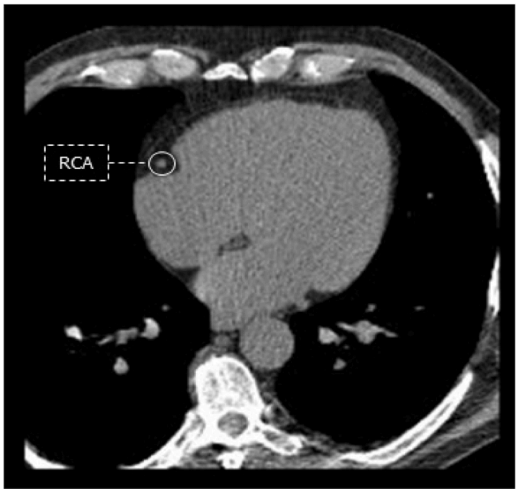

Fig. 3. Pericoronary epicardial fat volume measurement.
Pericoronary fat volume was measured along the vertical segment of the RCA in the atrioventricular groove. A cylinder with a radius of 5 mm and height of 15 mm was established around the artery, of which pericoronary fat volume.

Observers were also blinded to the HIV status and clinical data. For intra-observer agreement measurement, one observer repeated all measurements in a random subset of 40 participants, ≥ 1 month after the first assessment.

2.5. Observers

Observer 1 (IB) is a research assistant in the radiology department with 4-year experience in cardiac imaging postprocessing. Observer 2 (MS) is a physician and PhD student involved in the present study. Before starting postprocessing sessions, the two observers underwent a training session with a senior research assistant (5-year experience in cardiac imaging postprocessing) and a cardiothoracic radiologist (15-year experience) for epicardial fat quantification using 10 non-contrast cardiac CT examinations. These 10 examinations were not part of the present study cases.

2.6. Statistical analysis

All continuous variables were assessed for normal distribution. Normally distributed continuous data are presented as mean ± standard deviation. Non normally distributed data are presented as median [25th–75th interquartile range (IQR)]. Categorical data are presented as numbers and percentages. Epicardial fat values in the descriptive data are from observer 1. Inter-observer agreement for epicardial fat measurement including volume, area and thickness was assessed with the intraclass correlation coefficient (ICC) for absolute concordance of unique measurements, using a two-way random model. Intra-observer agreement was assessed with the intraclass correlation coefficient for absolute concordance of unique measurements, using a two-way mixed model [16]. An ICC < 0.40 implies poor agreement; 0.40–0.59, fair agreement; 0.60−0.74, good agreement and 0.75–1.00, excellent agreement [17]. Pearson's correlation coefficient was used to assess the association of epicardial fat measurements from observer 1 with BMI and DEXA-derived percentages of body fat. All analysis of reproducibility and correlation were stratified by HIV status, sex, BMI groups (normal < = 24.99 kg/m^2, overweight = 25−30 kg/m^2, obese > = 30 kg/m^2) and epicardial fat groups (epicardial fat threshold: Low < 134 cm^2, High > = 134 cm^2). A two-tailed p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS (SPSS version 24, IBM Corp., Armonk, NY, USA).

3. Results

3.1. Participants characteristics

167 HIV-infected and 58 non-HIV-infected participants were included in the present study. There was no significant difference in age and 10-year Framingham risk score between HIV-infected participants and non-HIV-infected participants, but HIV-positive participants were more likely to be males (93.4 (156/167) vs 75.9 (44/58) %, p = 0.001). HIV-infected participants showed lower BMI (25.3 ± 4.1 kg/m^2 vs 27.3 ± 4.0 kg/m^2 respectively, p = 0.002). Participant characteristics stratified by HIV status are described in Table 1.

Table 1
Participant's demographical and clinical characteristics.

	All participants (n = 225)	HIV-infected (n = 167)	Non-HIV-infected (n = 58)	P-Value
Age (years)	56.0 ± 7.4	55.8 ± 7.0	56.6 ± 8.3	0.540
Male	200 (88.9 %)	156 (93.4 %)	44 (75.9 %)	**0.001**
Diabetes	20 (8.9 %)	18 (4.8 %)	2 (3.5 %)	0.155
High blood pressure	70 (31.1 %)	53 (31.7 %)	17 (29.3 %)	0.858
Family history of CVD	46 (20.4 %)	35 (21.0 %)	11 (19.0 %)	0.892
Smoking (pack-years)	4.0 [0–21]	6.4 [0–26.3]	0.2 [0–8.8]	**0.004**
BMI (kg/m^2)	25.8 ± 4.2	25.3 ± 4.1	27.3 ± 4.0	**0.002**
Framingham risk score (%)	10 [7–15.3]	10.5 [7–16]	9 [7–15]	0.379

*Measurements are from observer 1. CVD : cardiovascular disease, BMI : body mass index. Normally distributed variables are expressed as mean ± standard deviation, non-normally distributed variables are expressed as median [Q1 – Q3], categorical variables are expressed using proportion (percentage).

3.2. Epicardial fat measurements and reproducibility

Mean epicardial fat volume was 134.4 ± 53.0 cm^3, mean epicardial fat area 108.0 ± 20.7 cm^2, mean epicardial fat thickness 17.9 ± 3.6 mm at the level of the RCA, and 6.6 ± 2.4 mm at the level of the LAD and mean pericoronary fat volume was 1.2 ± 0.4 mm^3 according to observer 1. There was no significant difference in crude epicardial fat measurements between HIV-infected and non-HIV-infected participants. However, adjusting for BMI showed epicardial fat volume, area and thickness, as well as pericoronary fat volume to be all significantly increased in HIV-infected participants compared to non-HIV-infected participants (all $p < 0.05$) (Table 2).

Table 2
Epicardial fat measurements results.

	All participants (n = 225)	HIV-infected (n = 167)	Non-HIV-infected (n = 58)	P-Value
Epicardial fat volume (cm^3)*	134.4 ± 53.0	137.5 ± 54.3	125.5 ± 48.4	0.139
Epicardial fat area (cm^2)*	108.0 ± 20.7	107.8 ± 21.8	108.5 ± 17.1	0.846
Epicardial fat thickness RCA (mm)*	17.9 ± 3.6	18.0 ± 3.4	17.4 ± 4.1	0.229
Epicardial fat thickness LAD (mm)*	6.6 ± 2.4	6.8 ± 2.4	6.1 ± 2.4	0.066
Pericoronary fat volume RCA (cm^3)*	1.2 ± 0.4	1.2 ± 0.4	1.1 ± 0.4	0.191
Epicardial fat volume indexed to BMI (cm^3/(kg/m^2))*	5.2 ± 1.8	5.4 ± 1.9	4.6 ± 1.7	**0.005**
Epicardial fat area indexed to BMI (cm^2/(kg/m^2))*	4.2 ± 0.7	4.3 ± 0.7	4.0 ± 0.7	**0.011**
Epicardial fat thickness RCA indexed to BMI (mm^3/(kg/m^2))*	0.7 ± 0.1	0.7 ± 0.1	0.6 ± 0.1	< **0.001**
Epicardial fat thickness LAD indexed to BMI (mm^3/(kg/m^2))*	0.3 ± 1.0	0.3 ± 0.1	0.2 ± 0.1	**0.004**
Pericoronary fat volume RCA indexed to BMI (cm^{33}/(kg/m^2))*	0.45 ± 0.02	0.05 ± 0.02	0.04 ± 0.02	**0.010**

* Measurements are from observer 1. RCA : right coronary artery, LAD : left anterior descending coronary artery. Normally distributed variables are expressed as mean ± standard deviation, non-normally distributed variables are expressed as median [Q1 – Q3], categorical variables are expressed using proportion (percentage).

The inter-observer agreement was excellent for epicardial fat volume (ICC = 0.75, 95 % CI, -0.03 – 0.91) and epicardial fat area (ICC = 0.95, 95 % CI, 0.83 – 0.98), good for thickness (ICC LAD = 0.64, 95 % CI, 0.55 – 0.71; ICC RCA = 0.64, 95 % CI, 0.55 – 0.71) and poor for pericoronary fat volume (ICC = 0.35, 95 % CI, 0.10 – 0.53) (Table 3).

The intra-observer agreement was excellent for epicardial fat volume (ICC = 0.97, 95 % CI, 0.93 – 0.98), epicardial fat area (ICC = 0.99, 95 % CI, 0.97 – 0.99) and epicardial fat thickness at the level of the LAD (ICC = 0.71, 95 % CI, 0.20 – 0.88), good for epicardial fat thickness at the level of the RCA (ICC = 0.68, 95 % CI, 0.25 – 0.92) and fair for pericoronary fat volume (ICC = 0.53, 95 % CI, 0.15 – 0.66) (Table 3).

In general, reproducibility showed slight to moderate variations when groups were stratified for sex (male, female), HIV status (HIV-infected and non-infected participants), BMI (normal, overweight, obese) and epicardial fat volume (highest half, lowest half). Tables 3A and 3B describes the inter-observer and the intra-observer agreement values for epicardial fat measurements in these stratified groups.

3.3. Correlation of epicardial fat quantitative data with BMI and DEXA-derived adiposity measurements

Almost all epicardial fat measurements were positively and significantly correlated to BMI in all participants (Table 4). Epicardial fat area had the highest correlation to BMI ($r = 0.53$, $p < 0.001$) while pericoronary epicardial fat volume had the lowest correlation to BMI ($r = 0.31$, $p < 0.001$). Epicardial fat thickness at the level of LAD was not significantly correlated to BMI ($r = 0.08$, $p = 0.277$). Results were similar when groups were stratified for HIV status (Tables 4A and 4B).

DEXA results were available for 173 participants who agreed to undergo this procedure, 135/173 (78.0 %) of them were HIV-infected and 38/173 (22.0 %) were non-HIV-infected. Correlation analyses of epicardial fat parameters with DEXA-derived percentages of body fat showed epicardial fat volume to be more correlated to total body fat ($r = 0.28$, $p < 0.001$) and to trunk fat ($r = 0.37$, $p < 0.001$) than area (Table 3). Correlation measures were consistently higher with trunk fat than with total body fat, and much lower with limb fat. Epicardial fat thickness at the level of LAD was not significantly correlated to DEXA-derived measures of body fat.

4. Discussion

The present study describes the reproducibility of different epicardial fat measurements on non-contrast cardiac CT and their correlation with other body fat indices in HIV-infected and non-HIV-infected patients. Our results show that CT quantification of epicardial fat volume and area is highly reproducible compared to thickness or pericoronary fat volume, in both the HIV-infected and non-HIV-infected groups. In addition, we have shown that epicardial fat volume correlates better with DEXA-derived total body fat and trunk fat than epicardial fat area, while epicardial fat thickness at the level of LAD does not correlate to BMI nor to body fat percentage.

Table 3
Inter-and intra-observer agreement for epicardial fat measurements.

	Inter-observer agreement, N = 225		Intra-observer agreement, N = 40	
	ICC	95 % CI	ICC	95 % CI
Epicardial fat volume	0.75	(-0.03 – 0.91)	0.97	(0.93 – 0.98)
Epicardial fat area	0.95	(0.83 – 0.98)	0.99	(0.97 – 0.99)
Epicardial fat thickness RCA	0.64	(0.55 – 0.71)	0.71	(0.20 – 0.88)
Epicardial fat thickness LAD	0.64	(0.55 – 0.71)	0.80	(0.25 – 0.92)
Pericoronary fat volume RCA	0.35	(0.10 – 0.53)	0.44	(0.15 – 0.66)

ICC : intraclass correlation coefficient, CI : confidence interval, RCA : right coronary artery, LAD : left anterior descending coronary artery.

Table 3A
Inter-observer agreement for epicardial fat measurements stratified by sex, HIV status, BMI and epicardial fat.

	Sex (female = 25, male = 200)			HIV status (HIV+ = 167, HIV- = 58)			BMI (normal = 100, overweight = 92, obese = 33)			Epicardial fat (Low = 131, high = 94)		
		ICC	95 % CI		ICC	95 % CI		ICC	95 % CI		ICC	95 % CI
EF volume	Female	0.76	−0.02 – 0.93−	HIV+	0.75	−0.40 – 0.92−	Normal	0.73	0.02 – 0.90	Low	0.46	−0.10 – 0.76−
	Male	0.75	0.04 – 0.92	HIV-	0.71	0.01 – 0.90	Overweight	0.66	−0.08 – 0.88−	High	0.55	0.09 – 0.83
							Obese	0.77	0.05 – 0.94			
EF area	Female	0.96	0.54 – 0.99	HIV+	0.95	0.81 – 0.98	Normal	0.92	0.76 – 0.96	Low	0.95	0.86 – 0.97
	Male	0.95	0.83 – 0.97	HIV-	0.93	0.85 – 0.97	Overweight	0.94	0.80 – 0.97	High	0.93	0.70 – 0.97
							Obese	0.94	0.54 – 0.98			
EF thickness RCA	Female	0.74	0.49 – 0.87	HIV+	0.63	0.53 – 0.71	Normal	0.64	0.51 – 0.75	Low	0.56	0.43 – 0.67
	Male	0.62	0.53 – 0.70	HIV-	0.65	0.46 – 0.78	Overweight	0.54	0.38 – 0.67	High	0.61	0.47 – 0.72
							Obese	0.65	0.41 – 0.81			
EF thickness LAD	Female	0.67	0.38 – 0.84	HIV+	0.65	0.56 – 0.73	Normal	0.75	0.65 – 0.83	Low	0.61	0.49 – 0.71
	Male	0.63	0.54 – 0.71	HIV-	0.54	0.33 – 0.70	Overweight	0.56	0.40 – 0.68	High	0.48	0.31 – 0.62
							Obese	0.47	0.15 – 0.70			
Peri-coronary fat volume	Female	0.31	−0.05 – 0.62	HIV+	0.36	0.11 – 0.54	Normal	0.45	0.21 – 0.63	Low	0.33	0.11 – 0.51
	Male	0.35	0.10 – 0.53	HIV-	0.30	0.00 – 0.54	Overweight	0.23	0.01 – 0.42	High	0.19	−0.03 – 0.39
							Obese	0.38	−0.08 – 0.69			

ICC : intraclass correlation coefficient, CI : confidence interval, RCA : right coronary artery, LAD : left anterior descending coronary artery, BMI thresholds: Normal < = 24.99, Overweight = 25−30, Obese > = 30, Epicardial fat threshold: Low < 134 cm^2, High > = 134 cm^2, Obese > = 30 kg/m^2, Epicardial fat threshold: Low < 134 cm^2, High > = 134 cm^2.

Table 3B
Intra-observer agreement for epicardial fat measurements stratified by sex, HIV status, BMI and epicardial fat.

	Sex (n = 40, female = 8, male = 32)			HIV status (n = 40, HIV+ = 21, HIV- = 19)			BMI (n = 40, normal = 14, overweight = 18, obese = 8)			Epicardial fat (Low = 131, high = 94)		
		ICC	95 % CI		ICC	95 % CI		ICC	95 % CI		ICC	95 % CI
EF volume	Female	0.91	0.22 – 0.99	HIV+	0.97	0.92 – 0.99	Normal	0.99	0.91 – 1.00	Low	0.87	0.43 – 0.96
	Male	0.97	0.94 – 0.99	HIV-	0.96	0.90 – 0.99	Overweight	0.93	0.87 – 0.98	High	0.93	0.83 – 0.97
							Obese	0.97	0.82 – 0.99			
EF area	Female	0.97	0.98 – 1.00	HIV+	0.99	0.98 – 1.00	Normal	0.98	0.93 – 0.99	Low	0.97	0.91 – 0.99
	Male	0.98	0.96 – 0.99	HIV-	0.98	0.94 – 0.99	Overweight	0.98	0.95 – 0.99	High	0.99	0.98 – 1.00
							Obese	0.94	0.97 – 1.00			
EF thickness RCA	Female	0.82	0.31 – 0.96	HIV+	0.63	−0.04 –	Normal	0.86	0.28 – 0.96	Low	0.71	0.35 – 0.88
	Male	0.66	0.12 – 0.86	HIV-	0.71	0.87	Overweight	0.54	0.05 – 0.81	High	0.62	−0.08 –
						0.30 – 0.89	Obese	0.60	−0.10 – 0.91			0.88
EF thickness LAD	Female	0.76	0.03 – 0.95	HIV+	0.79	0.03 – 0.94	Normal	0.65	−0.01 – 0.89	Low	0.58	−0.08 –
	Male	0.80	0.28 – 0.93	HIV-	0.82	0.45 – 0.93	Overweight	0.84	0.04 – 0.96	High	0.81	0.85
							Obese	0.86	0.49 – 0.97			0.43 – 0.93
Peri-coronary fat	Female	0.15	−0.63 –	HIV+	0.55	0.18 – 0.79	Normal	0.00	−0.03 – 0.08−0.08 –	Low	0.07	−0.31 –
volume	Male	0.50	0.75	HIV-	0.32	−0.08 –	Overweight	0.40	0.72−	High	0.65	0.46
			0.18 – 0.72			0.65	Obese	0.17	0.72 – 0.77			0.28 – 0.84

ICC : intraclass correlation coefficient, CI : confidence interval, RCA : right coronary artery, LAD : left anterior descending coronary artery, BMI thresholds: Normal < = 24.99, Overweight = 25−30, Obese > = 30, Epicardial fat threshold: Low < 134 cm^2, High > = 134 cm^2, Obese > = 30 kg/m^2, Epicardial fat threshold: Low < 134 cm^2, High > = 134 cm^2.

Table 4
Correlation of epicardial fat measurement with others fat measurements in HIV-infected and non-HIV-infected participants, N = 173.

	BMI		Percentage of total body fat		Percentage of trunk fat		Percentage of lower limb fat	
	Pearson rho	P-value	Pearson rho	P-value	Pearson rho	P-value	Pearson rho	P-value
EF volume	0.44	<0.001	0.28	<0.001	0.37	<0.001	0.06	0.416
EF area	0.53	<0.001	0.19	0.011	0.28	<0.001	0.04	0.603
EF thickness-RCA	0.36	<0.001	0.22	0.003	0.26	<0.001	0.12	0.112
EF thickness- LAD	0.08	0.277	0.03	0.659	0.08	0.296	−0.07	0.389
Pericoronary fat volume	0.31	<0.001	0.27	<0.001	0.32	<0.001	0.13	0.088

Correlation were measured using results from observer 1. EF: epicardial fat, BMI: body-mass index; percentage body fat: proportion of total mass that is fat mass; percentage trunk fat: proportion of the total mass of the trunk composed of fat; percentage trunk fat: proportion of the total mass of the trunk composed of fat; percentage lower limb fat: proportion of the total mass of the lower limbs composed of fat.

4.1. Inter- and intra-observer agreement of epicardial fat CT measurements

Our results on inter- and intra-observer reproducibility are consistent with previous studies in the non-HIV-infected population showing that quantification of epicardial fat volume and area are highly reproducible [14,18,19]. Using CT, Gorter et al. [14] reported a high reproducibility for total epicardial fat volume and a moderate reproducibility for epicardial fat area and thickness. Similar results were seen for the quantification of epicardial fat using magnetic resonance [19]. Our data shows a higher inter-observer agreement for epicardial fat area measurement than for epicardial fat volume. However, given the significant inter-individual differences in the global distribution of epicardial fat, this quantification method may not necessarily reflect total epicardial

Table 4A
Correlation of epicardial fat measurement with others fat measurements in HIV-infected participants, N = 135.

	BMI		Percentage of total body fat		Percentage of trunk fat		Percentage of lower limb fat	
	Pearson rho	P-value	Pearson rho	P-value	Pearson rho	P-value	Pearson rho	P-value
EF volume	0.47	<0.001	0.36	<0.001	0.43	<0.001	0.14	0.112
EF area	0.56	<0.001	0.28	0.001	0.34	<0.001	0.13	0.131
EF thickness-RCA	0.42	<0.001	0.29	0.001	0.31	<0.001	0.22	0.012
EF thickness- LAD	0.13	0.140	0.10	0.248	0.14	0.114	0.001	0.989
Pericoronary fat volume	0.40	<0.001	0.37	<0.001	0.40	<0.001	0.23	0.007

Correlation were measured using results from observer 1. EF: epicardial fat, BMI: body-mass index; percentage body fat: proportion of total mass that is fat mass; percentage trunk fat: proportion of the total mass of the trunk composed of fat; percentage trunk fat: proportion of the total mass of the trunk composed of fat; percentage lower limb fat: proportion of the total mass of the lower limbs composed of fat.

Table 4B
Correlation of epicardial fat measurement with others fat measurements in non-HIV-infected participants, N = 38.

	BMI		Percentage of total body fat		Percentage of trunk fat		Percentage of lower limb fat	
	Pearson rho	P-value	Pearson rho	P-value	Pearson rho	P-value	Pearson rho	P-value
EF volume	0.51	0.002	0.26	0.112	0.39	0.017	0.08	0.637
EF area	0.52	0.001	−0.06	0.704	0.09	0.559	−0.21	0.208
EF thickness-RCA	0.28	0.104	0.18	0.290	0.24	0.142	0.04	0.825
EF thickness- LAD	0.15	0.378	0.19	0.258	0.22	0.190	0.11	0.498
Pericoronary fat volume	0.12	0.495	0.28	0.094	0.31	0.062	0.19	0.263

Correlation were measured using results from observer 1. EF: epicardial fat, BMI: body-mass index; percentage body fat: proportion of total mass that is fat mass; percentage trunk fat: proportion of the total mass of the trunk composed of fat; percentage trunk fat: proportion of the total mass of the trunk composed of fat; percentage lower limb fat: proportion of the total mass of the lower limbs composed of fat.

fat as it is obtained on a single slice. One other finding is that epicardial fat thickness measurement was associated with only moderate reproducibility and this may be explained by slice selection variability by the operator. Of note, the very low CT attenuation of fat as compared to other nearby cardiac structures makes this modality very accurate in comparison to cardiac ultrasound or magnetic resonance for the quantification of epicardial fat. Also, studies have shown that the accuracy of epicardial fat CT assessment methods is maintained even when aggressive CT radiation dose reduction strategies recently developed are used [20,21].

4.2. Correlation with other body adiposity measurements

Correlation of the different epicardial fat measurement methods with other body fat indices has not been well explored previously. Our data shows epicardial fat volume to be the most correlated to DEXA-derived total body and trunk fat in all participants, as well as in the HIV-infected and non-HIV-infected groups. In contrast, it is epicardial fat area that best correlates to BMI. However, although BMI is the most frequently used method to assess adiposity, its major limitation is its low power to discriminate between weight due to adipose tissue from weight associated to muscle mass. DEXA is more accurate and precise and provides measurement of total body fat mass as well of fat mass in specifically defined regions with a good correlation with adiposity measurement obtained with CT [22,23]. In addition, growing evidence suggest that visceral adiposity, defined as fat in the trunk and abdomen, confers a much higher cardiovascular risk than general obesity or subcutaneous adiposity [24–28]. This suggest that the epicardial fat volume method should be preferred over the area method when quantifying this adipose tissue.

4.3. Strengths and limitations

In the present study, we evaluated the reproducibility of epicardial fat measurements on non-contrast cardiac CT. One important strength of cardiac CT for the assessment of epicardial fat is that it also allows to measure coronary calcium score, using the same data set and without additional radiation exposure. Using one imaging modality, studies may evaluate the association of epicardial fat with coronary artery disease as coronary calcium score has been shown to be a marker of coronary artery disease in the general and HIV populations [29,30]. Other strengths of the study include its sample size, as well as the independent assessments of epicardial fat by two observers and the blinding to other evaluator's results and HIV status. We also studied correlations of epicardial fat to both DEXA-derived body fat percentages and BMI, two different indicators of general and regional adiposity.

Our study has some limitations. Epicardial fat CT segmentation is moderately time consuming, requires training as well as the use of an advanced cardiac imaging software. These are limits to a large-scale use of this methodology. Our study was also limited to one center using one specific cardiac scanner and one software package. Further validation may be required to apply the results to other hardware/software combinations. For example, in their study, Maurovich-Horvat et al. [31] reported an excellent reproducibility when assessing pericoronary fat volume along a 4-cm long-axis distance using contrast-enhanced CT while our measure of pericoronary fat volume had a poor reproducibility. Finally, the cross-sectional design of our study did not allow to assess rates of change in epicardial fat volume.

5. Conclusion

In summary, the present study demonstrates a high reproducibility of epicardial fat volume and area measurement using CT. Epicardial fat volume measurement shows a superior correlation with DEXA-derived total body or trunk fat percentages and should be considered over area or thickness-based assessment methods when quantifying epicardial fat. Futures studies could use epicardial fat volume quantification when assessing the interaction of epicardial fat with HIV-specific factors and its role in the development of coronary artery disease in HIV patients.

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Ethical statement

Study approval was obtained from the institutional review board of the CHUM (University of Montreal Medical Center) and participating centers and all participants gave written informed consent.

Contribution of authors

Sadouni M: Data collection, statistical analysis, manuscript writing and revision

Boldeanu I: Data collection, statistical analysis

Durand M: Study design, manuscript revision

Daniel Juneau: Data collection, manuscript revision

Tremblay C: Study design, manuscript revision

Chartrand-Lefebvre C: Study design, data collection, statistical analysis, manuscript writing and revision.

Declaration of Competing Interest

Authors have no conflict of interest to declare.

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