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Journal

Journal of Cardiovascular Computed Tomography, 14(1)

ISSN

1934-5925

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Publication Date

2020

DOI

10.1016/j.jcct.2019.05.004

Peer reviewed

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Author manuscript
J Cardiovasc Comput Tomogr. Author manuscript; available in PMC 2021 January 01.

Published in final edited form as:
J Cardiovasc Comput Tomogr. 2020 ; 14(1): 55–59. doi:10.1016/j.jcct.2019.05.004.

Non-Contrast Cardiac CT-based Quantitative Evaluation of Epicardial and Intra-Thoracic Fat in Healthy, Recently Menopausal Women: Reproducibility Data from the Kronos Early Estrogen Prevention Study

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Abstract

Background: Cardiac fat is emerging as an important parameter for cardiovascular risk stratification. Accurate and reproducible volumetric measurements can facilitate in the serial assessment of cardiac fat by computed tomography (CT). We assessed the intra- and inter-observer variability of cardiac fat volumetric measurements using a semi- automated CT software.

Methods: We used non-contrast coronary calcium CT scans to quantify epicardial and intra-thoracic fat volumes. Two expert readers analyzed baseline and follow up CT scans of 45 subjects by using a semi-automated CT software (QFAT 2.0, Cedars Sinai- Medical Center). Correlation and Bland-Altman analysis was performed for both intra- and inter-observer comparisons for each cardiac fat type.

Results: The intra-observer correlation coefficients ranged between 0.86 to 0.99 and 0.87 to 0.99 for epicardial (median fat per reader (cm^3) 20.9 to 25.7) and intra-thoracic (median fat per reader

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Clinical Trial Registration: URL: https://www.clinicaltrials.gov. Unique identifier: NCT00154180

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Conflicts of Interest
Dr. Budoff receives grant support from General Electric. We wish to confirm that the other authors have no known conflicts of interest associated with this publication.

(cm^3) 27.1 to 31.6) fat volumes respectively, with no significant differences between individual data points (all p>0.38). The inter-observer correlation coefficient was 0.99 (p<0.0001 for correlation) for both epicardial and intra-thoracic fat. By Bland-Altman analysis for epicardial fat measurements, mean difference of intra- observer was 0.90 cm^3 with 95% confidence intervals (0.22,1.7) and −1.8 cm^3 for inter- observer, with 95% CI (−2.9, −0.69). Bland-Altman plots for intra-thoracic fat measurements were similarly impressive for both inter- and intra-observer reads.

Conclusions: Our data showed that measuring epicardial and intra-thoracic fat volumes by CT using a semi-automated software has excellent intra-observer and inter-observer reliability. Cardiac fat volumes can be obtained easily and reproducibly from routine calcium scoring scans and may help in assessing cardiovascular risk.

Keywords

Epicardial fat volume; intra-thoracic fat volume; computed tomography; intra-observer; inter-observer

1. Introduction

Recent studies have investigated ectopic fat changes in the heart and its pathogenic role in the inter-related immune mechanism of atherosclerosis. Excess fat in the epicardium may accelerate coronary atherosclerosis by releasing proinflammatory cytokines.[1,2] Epicardial fat is reported to be associated with coronary calcification,[3]myocardial ischemia,[4] inflammation and is an independent predictor of adverse cardiovascular events.[5] A standardized and robust method to quantify cardiac fat has not been previously established but would have utility in the clinical setting.

Cardiac fat volumetric measurements can be performed on the same non-contrast cardiac computed tomography (CT) scans, typically used for coronary calcium scoring. We measured two types of cardiac fat depots: epicardial fat volume (EFV), which is enclosed by the visceral pericardium and intra-thoracic fat volume (IFV), which surrounds the parietal pericardium.[6,7] The purpose of this study was to assess intra- and inter-observer variability of EFV and IFV by using a semi-automated post-processing cardiac CT software (QFAT 2.0, Cedars Sinai-Medical Center).

2. Materials and Methods

2.1 Study Population

Data in this study was gathered from screening visits of KEEPS (**K**ronos **E**arly **E**strogen **P**revention **S**tudy) performed at nine centers. The KEEPS prospectively examines the effects of menopausal hormone therapy on subclinical atherosclerosis and cardiac fat changes over four years. Clinical, biochemical and non-contrast cardiac CT data were collected from healthy, post-menopausal women (mean age 52.9±2.6 years) without known cardiovascular disease.[9] Participants were double-blinded and randomized to either two active treatment groups (oral or transdermal hormone therapy) or placebo. A subset of the KEEPS population was assessed to determine the reliability of the technique used for cardiac fat measurement. The study was approved by institutional review board in LA Biomedical Research Institute

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at Harbor-UCLA. In total, 45 participants were used in the analysis (15 per intra- and inter-observer samples). Table 1 lists the patient characteristics at the baseline visit date.

2.2 Cardiac Fat Measures

A previously described methodology was used to perform EFV and IFV measurements in baseline and follow up CT scans of each participant.[8,9] KEEPS participants were scanned using either Electron Beam CT (C150XP or C300 Electron Beam CT Scanners) or Electron Multidetector CT (GE Helical Scanner or Siemens Multi-Slice Scanner) with prospective ECG-triggering, and a tube voltage of 120 kVp; slice thickness was either 1.5, 2.5 or 3.0 mm, depending on the scanner.[10] Two experienced readers independently analyzed each scan twice with a time interval between the readings of at least one week. Both readers were blinded to subject characteristics and clinical data. Inferior and superior limits of the heart were defined as 10 mm above and 30 mm below the left main (LM) coronary artery. Contour and slice limits were manually corrected. About 6 to 8 control points were placed bordering the pericardium every 2 to 3 slices and the software automatically calculated IFV (Fig. 1). A threshold of −190 to - 30 Hounsfield Units (HU) differentiated fat from surrounding tissue, where higher HU were indicative of more fat.[9]

2.3 Statistical Analysis

The sample was randomized into intra- and inter-observer groups using the SAS software, version 9.4 (SAS Institute Inc., North Carolina) and assumed to have a normal distribution.

Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as N (%). Differences between samples were tested with independent samples t-test. A p-value <0.05 was considered statistically significant.

All statistical analyses were performed using MedCalc Statistical Software for Windows, version 18.6 (MedCalc Software bvba, Belgium). Statistical correlations for intra- and inter-observer comparisons were analyzed by Pearson correlation coefficient. By the Bland-Altman method, the mean difference between two reads or readers were calculated for each cardiac fat type and 95% confidence intervals as the mean difference were reported.

3. Results

For intra- and inter-observer comparisons, correlation coefficients were calculated to determine the association between reads. The intra-observer correlation coefficients between repeated readings of epicardial and intra-thoracic fat were remarkably high ($r = 0.86$ and 0.99, respectively for epicardial fat; and 0.87 and 0.99, respectively for intrathoracic fat). Median fat per reader (cm^3) ranges were calculated to be 20.9 to 25.7 and 27.1 to 31.6 for epicardial and intra-thoracic fat, respectively. Similarly, the inter- observer correlation coefficients between readers for both cardiac fat types were also high ($r = 0.99$ each for both epicardial and intra-thoracic fat). There was no statistical difference between samples (all p-values > 0.38).

The Bland-Altman method was used to further show the agreement between quantitative methods of cardiac fat volumetric measurements for all the reads (Table 2). As shown in

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Figures 2 and 3, there was very good agreement between paired data for both intra- and inter-observer comparisons.

4. Discussion

Increased EFV and IFV are positively correlated with the presence and progression of coronary plaque.[11] Excess fat deposits in the heart can become cardio-toxic contributing to considerable inflammatory changes and overall cardiac dysfunction.[12] This evidence warrants consideration that cardiac fat can be an imaging marker with added prognostic significance, as we have demonstrated this represents an accurate method to quantify fat volumes.

We used a method previously described by Huang G. et al and Ding J. et al for EFV and IFV measurements in non-contrast cardiac CT. The results of our study showed low intra- and inter-observer variability of both cardiac fat types (r =0.86 to 0.99 for epicardial fat;0.87 to 0.99 for intra-thoracic fat), which are consistent with the findings reported in previous studies.[8,9,13]

The median fat per reader for EFV and IFV were 20.9 to 25.7 and 27.1 to 31.6 cm^3, respectively. Other investigators have reported these fat volumes in women to be significantly higher.[14, 15] This observed variance may be explained by the discrepant or ambiguous definitions of cardiac fat types, whether total as oppose to partial volumes were analyzed and whether patients have coronary atherosclerosis.

Non-contrast cardiac CT offers a robust method to compute both cardiac fat types and complete the overall analysis within 2–3 minutes with very little manual adjustment of fat contours. Therefore, this non-labor intensive computer-assisted software may serve as an efficient method of quantifying cardiac fat volumes in large multi-center prospective clinical studies or even clinical evaluations.

5. Limitations

The study may have been limited by its small sample size (n=45), retrospective design and lack of correlation with clinical outcomes, and the uniform population, all patients enrolled in KEEPS were healthy peri-menopausal women. The use of baseline and follow up CT scans for measurements may have weakened the observed agreements for intra- and inter-observer fat measures. The reliability and feasibility in other populations may require further validation as the KEEPS participants were a priori a healthy group.

6. Conclusions

EFV and IFV can be obtained easily and reproducibly from routine coronary calcium scans and may help improve cardiovascular risk assessment. A quantitative fat volume measurement using a semi-automated CT software is important to accurately understand and monitor the relationship between cardiac fat and the course of atherosclerosis.

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Acknowledgments

Sincere thanks to all the physicians and students who have supported me in the past years, in particular to Dr. Matthew Budoff, Dr. Dong Li, Dr. Rine Nakinishi, Dr. Damini Dey and Dr. Ann E Kearns for their guidance and mentorship in the writing of this data. I am also grateful to Dr. Dong Li and Dr. Youngju Pak who provided expertise for understanding biostatistics. Lastly, I thank my parents for always supporting my endeavors.

8. Funding Statement

Funding for our work and QFAT software was provided by Dr. Damini Dey from Cedars- Sinai Medical Center, Los Angeles CA using a NIH/NHLBI grant 1R01HL133616–01.

Abbreviations

CAD	Coronary Artery Disease
CT	Computed Tomography
EFV	Epicardial Fat Volume
IFV	Intra-thoracic Fat Volume
KEEPS	Kronos Early Estrogen Prevention Study
CAC	Coronary Artery Calcium
HU	Hounsfield Units

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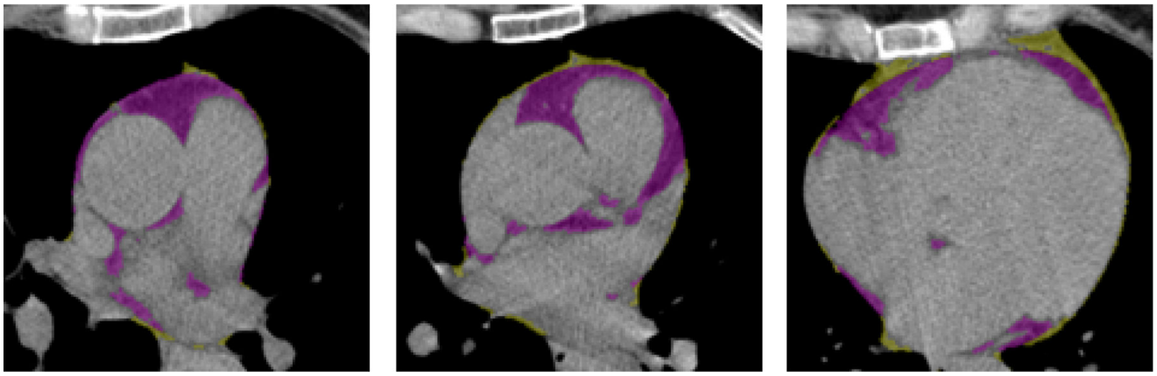

Figure 1. Cross-sectional views showing epicardial (purple contour) and intrathoracic fat (yellow contour)

Fig. 1 shows CT slices inferiorly, at the level of the LM and superiorly.

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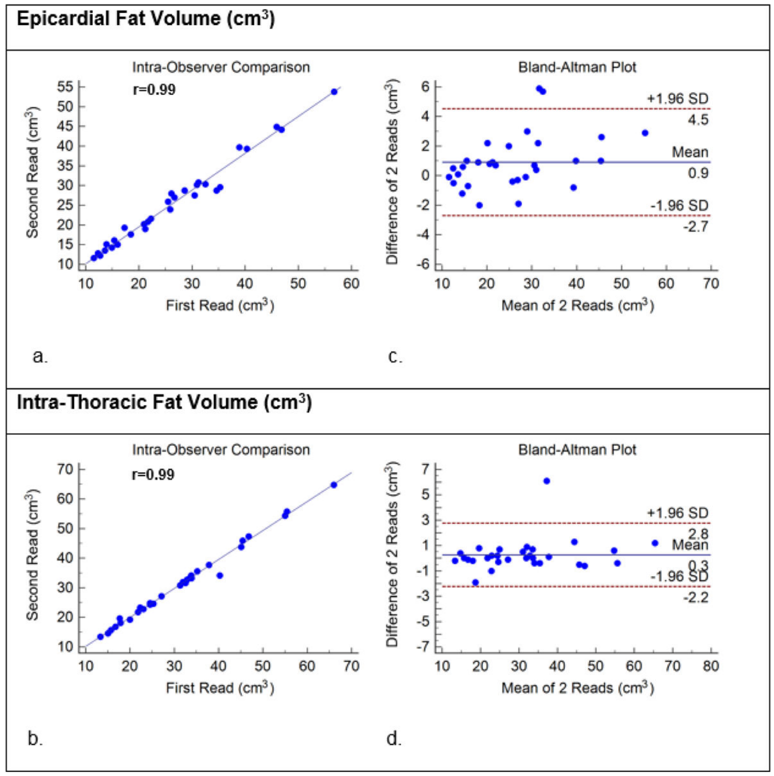

Figure 2. Intra-observer reliability for first reader

Figures a and b (left) show scatter plots of Reader 1's first and second reads for each of the 30 selected scans for EFV and IFV, respectively. Figures c and d (right) show Bland-Altman plots of the differences of the two reads versus the means of the two reads for each cardiac fat volume.

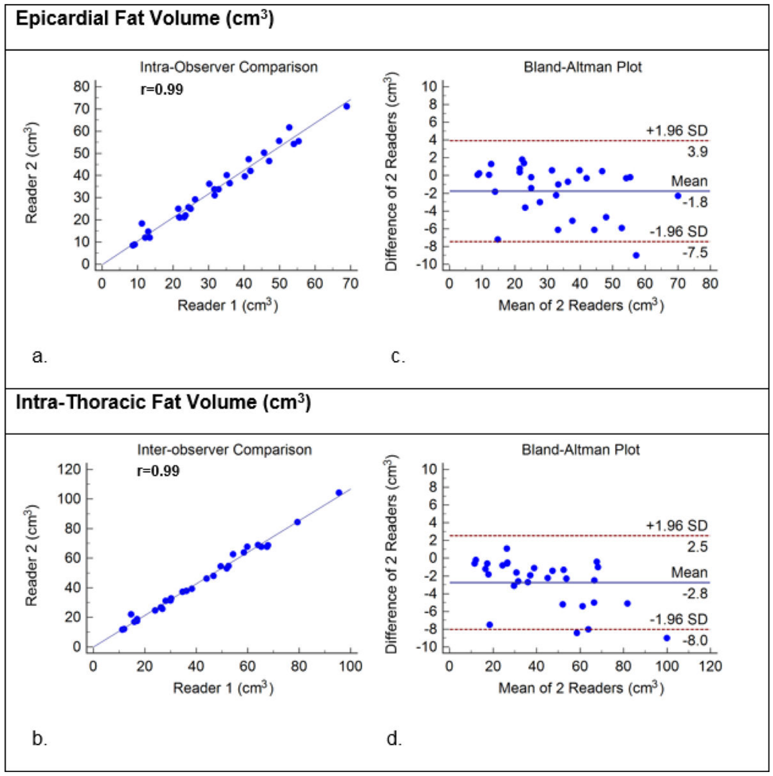

Figure 3. Inter-observer reliability

Figures a and b (left) show scatter plots of Reader 1 and Reader 2’s first reads for each of the 30 selected scans for EFV and IFV, respectively. Figures c and d (right) show Bland-Altman plots of the differences of the two reads versus the means of the two reads for each cardiac fat volume.

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Table 1.

Patient Characteristics

Characters	Values (n=45)
Age (years) *	52±2.6
BMI (kg/m^2) *	25.7±4.2
Waist Circumference (cm) *	83.4±11.2
Hypertension	5 (11.1%)
Diabetes	0 (0%)
Current Smokers	2 (6.25%)
Family History of CAD: Mother	5 (12.5%)
Family History of CAD: Father	6 (15%)
Hypercholesterolemia	2 (6.25%)
Angina	0 (0%)
Triglycerides (mg/dL) *	73.6±29.3
LDL-C (mg/dL) *	114.6±31
HDL-C (mg/dL) *	79.4±13.8

* data is reported as mean±SD

BMI = Body Mass Index; CAD = Coronary Artery Disease; LDL-C = Low Density Lipoprotein Cholesterol; HDL-C = High Density Lipoprotein Cholesterol

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Table 2.

Bland-Altman results for intra- and inter-observer comparisons of cardiac fat volumes

	Intra-Reader 1		
	Mean Diff	95% CI	95% LOA
Cardiac Fat Types			
Epicardial Fat	0.90	0.22, 1.7	−2.7, 4.5
Intra-thoracic Fat	0.26	−0.22,0.7	−2.2, 2.8
	Intra-Reader 2		
	Mean Diff	95% CI	95% LOA
Cardiac Fat Types			
Epicardial Fat	−2.4	−5.2, 0.30	−16.9,12.0
Intra-thoracic Fat	−3.4	−6.7,−0.23	−20.3, 13.5
	Inter-Reader		
	Mean Diff	95% CI	95% LOA
Cardiac Fat Types			
Epicardial Fat	−1.8	−2.9,−0.69	−7.5, 3.9
Intra-thoracic Fat	−2.8	−3.8, −1.8	−8.0, 2.5

Mean Diff = Mean Difference; CI = confidence interval; LOA = limits of agreement