Measurement of Epicardial Fat Using Non-contrast Routine Chest-CT: A Consideration of Threshold Adjusting for Fatty Attenuation

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Research Article

Keywords: Computed tomography, Atherosclerosis, Epicardial fat volume, Epicardial fat attenuation, Coronary artery disease

Posted Date: May 25th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-514818/v1

Abstract

Background Role of epicardial fat (EF) had expended from a marker of cardiovascular risk to indicators of several systemic physiological effects and needed to be measured in more scenarios. The present study aimed to determine whether the EF volume (EFV) and mean attenuation (EFA) measured on non-contrast routine chest-CT (RCCT) could be more consistent with that on coronary CT angiography (CCTA) by adjusting the threshold of fatty attenuation.

Methods: Totally 83 subjects simultaneously underwent CCTA and RCCT were enrolled. EFV and EFA were quantified on CCTA using threshold of (N30) (-190HU, -30HU) as reference, and also measured on RCCT using threshold of N30, N40 (-190HU, -40HU), N45 (-190HU, -45HU) respectively. Correlation and agreement of EF metrics between two models and differences between groups with coronary plaque (Plaque (+)) and without plaque (Plaque (-)) were analyzed.

Results: EFV and EFA from RCCT using N30, N40 and N45 correlated well with reference (EFV: r^2=0.974, 0.976, 0.972, P<0.001; EFA: r^2=0.516, 0.500, 0.477, P<0.001). Threshold adjusting was able to reduce the mean difference, while increase the difference of EFA. Data measured on CCTA and RCCT both demonstrated the significantly larger EFV of Plaque (+) group than Plaque (-) group (*P*<0.05). The significantly difference of EFA was only shown on RCCT using N30 (Plaque (+) vs (-): -80±4.4HU vs-78±4HU, *P*=0.030).

Conclusion: The consistency of EFV measured on RCCT could be improved through adjustment of attenuation threshold. The EFA assessment may have additional information relating to underlying pathophysiological status.

Background

The visceral fat located between the myocardial surface and the visceral layer of pericardium known as epicardial fat (EF) is well known as an important imaging indicator for cardiovascular risk stratification[1]. Evidence during the last two decades show that EF play various regulating roles relating to cardiac biology including atherosclerosis progression, atrial fibrillation and heart failure[2-5]. EF also acts as a paracrine or vasocrine organ by locally releasing bioactive cytokines into the adjacent interstitium of the myocardium and coronary arteries[6]. The underlying complex and important functions relating to metabolic, thermogenic and mechanical properties, and the relationship to non-cardiac organ and systemic diseases are getting more and more attention [6]. The amount of EF is reported as a good predictor of risk of metabolic syndrome and an appealing biomarker to evaluate efficacy of certain therapy, such as pharmacological therapies for obesity, dyslipidaemia and type 2 diabetes mellitus[6-8]. On the other hand, cardiac involvement in the Coronavirus Disease 2019 (COVID-19) pandemic has been demonstrated[9]. With high level of angiotensin-converting enzyme 2(ACE2) expression, EF is suspected to be an important mediator of the inflammatory response in myocardium after SARS-CoV-2 infection[10, 11]. All those are looking forward to a approach to quantifying EF consistently and economically.

Cardiac examinations such as echocardiography, coronary CT angiography (CCTA) and coronary calcium score (CCS) are most commonly used imaging models to assess EF amount currently[12, 13]. However, there are situations in which participant is not necessary to have specific cardiac examination, such as assessment of young population for the reference values of EF measurements, or prognostic prediction of patients with metabolic diseases. In these scenarios, routine chest CT (RCCT) imaging can also be used to quantify volume of EF (EFV), especially the routinely performed non-contrast RCCT. When using the same threshold of fatty attenuation, EFV measured on RCCT correlates well with that on CCTA but is overestimated[14]. Besides, the EF attenuation (EFA) as a measures of fat composition[15, 16] has not been compared between the two imaging models. Therefore, the present study aimed to determine whether the EFV and EFA measured on RCCT by adjusting the threshold of fatty attenuation could be more consistent with that on CCTA based on the same scanner.

Materials And Methods

Subject selection

All subjects who underwent coronary CT angiography (CCTA) and non-contrast RCCT simultaneously for health check-up in our center from January 2019 to August 2020 were retrospectively investigated. Those who underwent surgery or invasive procedure of lung, mediastinum and heart were excluded. Total of 83 subjects were ultimately enrolled in this study. Information about sex, age, diabetes, dyslipidemia, and hypertension were collected from their records. This retrospective study was approved by the institutional review board. All participants were fully informed and agree that their medical records will be anonymized for research purposes.

CT Examination Procedure

The CCTA and RCCT scanning were performed on the same 320-slice CT scanner (uCT960+, Shanghai United Imaging Healthcare) simultaneously without change in position. RCCT parameters were as follows: 120 kVp; 300 mAs; detector collimation, 160 × 0.5; pitch, 1.0938; rotation time, 0.5 s; matrix size, 1024 × 1024; field of view, 350 mm; and slice thickness, 1.0 mm, covering the scanning range from the lung apices to the bases. Subsequently, CCTA were performed using a breath-hold prospective axial ECG-triggered acquisitioning protocol. For patients with heart rate >65 beat/min, metoprolol was taken orally about 1-1.5 hours before CCTA examination. Sublingual nitroglycerine (0.5mg) was administered 5 min before scanning, except in the case of contraindications. Intravenous injection of iodinated contrast medium was injected through the right cubital vein with a double cylinder high pressure syringe (370mgI/ml, flow rate :4.0-5.0ml/s, the total amount of injection was 0.8ml/kg) followed by saline (25ml) injected at the same flow rate. The scan was obtained from the carina to the heart bottom, and Bolus Tracking automatic trigger scanning technology was used, the monitoring layer is located at the center of the scanning range, the ROI is placed at the center of the descending thoracic aorta, the triggering threshold is set at 120HU, and the scanner will delay 6s to start scanning automatically after reaching the

threshold. The parameters were as follows: 100 kVp; 120 mAs; detector collimation, 320 × 0.5; pitch, 1.0938; rotation time, 0.25 s; matrix size, 512× 512; field of view, 350 mm; and slice thickness, 0.5 mm.

Assessment of CCTA

All the images were imported from the Picture Archiving and Communication System to the postprocessing workstation (uWS-CT, R004, Shanghai United Imaging Healthcare). Both the cross-sections and longitudinal reconstructed images were visually inspected to detect coronary plaques by two radiologists with 10 and 15 years of experience in cardiac imaging analysis. The presence of atherosclerotic plaques and stenosis grading were evaluated based on 18 segments model recommended by SCCT[17]. Stenosis grading used the 6 levels scale as follow: 1-Normal, absence of plaque and no luminal stenosis; 2-Minimal, plaque with <25% stenosis; 3-Mild, 25% to 49% stenosis; 4-Moderate, 50% to 69% stenosis; 5-Severe, 70% to 99% stenosis; 6-Occluded. Structures clearly assignable to the vessel wall on at least two views with densities less than the lumen contrast were classified as non-calcified plaque. Any structure with a density ≥130 HU that could be visualized separately from the contrast-enhanced coronary lumen was defined as calcified plaque, which including calcified and partially calcified ones. Patients with any form of plaques including noncalcified, calcified one were defined as plaque positive (Plaque (+)) group. The others were defined as plaque negative (Plaque (-)) group.

Measurement of EF

EF was defined as the visceral fat between the myocardial surface and the visceral layer of the pericardium. (Figure 1a-b.) The pericardium was manually traced from bifurcation of the pulmonary trunk to the end of the pericardial sac. The interested volume of whole heart and the frequency table of CT value within was generated and exported to personal computer. Threshold of fat tissue was applied to define the fat-containing voxels. EF volume (EFV, reported in cm^3) equals to the product of volume of single voxel and number of fat-containing voxels. EFA (reported in HU) defined as the mean attenuation of all fat-containing voxels. Attenuation histogram was reviewed to show the distribution of fat-containing voxels. Threshold of -190 to -30 Hounsfield units (HU) (-190HU, -30HU) was applied to extract the fat-containing voxels for CCTA image. While for the RCCT, the lower threshold was fixed at -190HU, and upper threshold was adjusted and set at -30HU (N30), -40HU (N40) and -45HU (N45). The measured EFV and EFA in corresponding threshold were recorded as EFV_{N30} and EFA_{N30}, EFV_{N40} and EFA_{N40}, EFV_{N45} and EFA_{N45}, respectively.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as N (%). Measurement data on CCTA was compared with that on RCCT using the paired t test. Correlations and agreement of EF measurements between RCCT and CCTA scan were evaluated using Pearson’s correlation test and Bland–Altman analysis. The difference of EF according to the presence or

absence of coronary atherosclerosis plaque were analyzed using Student's t-test, Mann–Whitney U test or chi-squared test.

Results

Among all the 83 subjects enrolled, 49 subjects (59.0%) had no plaque nor luminal stenosis in the CCTA. Plaques were detected in the other 34 (41.0%) subjects, in which 9(26.5%), 18(52.9%), 5(14.7%), 1(2.9%) and1(2.9%) subjects had minimal, mild, moderate, severe stenosis and occluded. Among the patients with plaques, 24 subjects (70.6%) with calcified plaques, 10 subjects (29.4%) with non-calcified plaques. Regarding the number of involved coronary artery segments, 17 subjects (50.0%) with only 1 segment, 7 subjects (20.6%) with 2 segments, 5 subjects (14.7%) with 3 segments, and 5 subjects (14.7%) with 4 segments. The general characteristics are shown in Table.1.

Comparison of EF measurements between CCTA and RCCT

Visually, the pericardial structure in RCCT could be identified as clearly as CCTA (Figure 1a-b.). Attenuation histogram of fat tissue revealed similar curve patterns that the right end was about 20-30 times higher than the left end (Figure 1c-d). When using the same threshold of (-190HU, -30HU), both EFV and EFA measurement correlated well with each other (r2= 0.974, 0.516) (Figure 2a, 3a). Bland–Altman analysis showed the mean difference (95% LoA) of EFV and EFV_{N30} was -15.2 (-29.7 to -0.6) cm^3, which suggesting an overestimate about 15.2% in RCCT compared with CCTA using the same threshold (Figure 2c). While the agreement of EFA between CCTA and RCCT was good, the mean difference (95% LoA) of EFA and EFA_{N30} was 0 (-6.1 to 6.2)HU (Figure 3c) .

Effect of threshold adjustment on EF measurement

After the adjusting, EFV_{N40} and EFV_{N45} still correlated excellently with EFV in CCTA (r2=0.976, 0.972, P<0.001) (Figure 2b-c.). Bland–Altman analysis showed the mean difference (95% LoA) of EFV and EFV_{N40}, EFV_{N45} were -3.3 (-15.9 to 9.4) cm3, 1.9 (-11.1 to 14.8) cm3, respectively (Figure 2d-f.). The use of threshold adjusting was able to reduce the bias of FFV from -15.2 cm3 to -3.3 cm3 or 1.9 cm3. EFA in RCCT using adjusted thresholds (EFA_{N30}, EFA_{N40}, EFA_{N45}) correlated well with EFV in CCTA (r2=0.516, 0.500, 0.477, P<0.001) (Figure 3a-c.). The mean difference (95% LoA) of EFA and EFA_{N30}, EFA_{N40}, EFA_{N45} were 0 (-6.1 to 6.2)HU, 5.2 (-0.6 to 11.1)HU, 7.4 (1.6 to 13.3)HU, respectively (Figure 3d-f.). Although there were good correlation and agreement between EFA measured on the two imaging models, the correlation coefficient decreased and the bias increased appropriately after threshold adjusting.

Comparison of EF measurements based on presence of plaques

Results of EF measurements based on the CCTA image showed that the EFV in the Plaque(+) group (115.6±44.1cm^3) was significantly larger than that of Plaque(-) group (88.9±28.6cm^3, P=0.003), the EFA between the two groups were similar (Plaque(+) vs (-): -79.5±3.8HU vs -78.3±4.2 HU, P=0.204) (Table 1).

When using the RCCT image and same attenuation thresholds, the EFV_{N30} of the Plaque(+) group was significantly larger than that of Plaque(-) group (131.2±49.6cm^3 vs 103.7±31.2cm^3, P=0.008). In this setting, the EFA_{N30} of the Plaque(+) group was significantly lower than that of Plaque(-) group (-80±4.4HU vs -78±4HU, P=0.030)(Figure 4b.). After adjusting of the attenuation threshold to N40 and N45, the differences of EFV between Plaque(+) and Plaque(-) group was still significant (P=0.006 and 0.009, respectively), but those of EFA were not shown (P=0.092 and 0.075, respectively). (Figure 4.)

Discussion

The present study validated again that non-contrast RCCT could be used to quantifying EFV and EFA, although EFV might be overestimated when using the same upper threshold of -30HU as most previous studies used. Through adjusting of the upper threshold, the consistency of EFV measured on RCCT could be improved substantially, while not for EFA. The measurement of EF based on non-contrast RCCT imaging was sensitive to detect the differences of EF characteristics between the groups with or without coronary plaque. Quantification of EFA might be more sensitive in revealing latent pathophysiological characteristics.

ECG-gated cardiac-CT was considered to be the most accurate method to quantified EFV because of the high resolution and true volume coverage, though which EFA could be obtained simultaneously[18, 19]. When CT was used to measure fat, segmentation of pericardium and the following filter of pixels with specific attenuation threshold of fat are two necessary steps measuring EF, the former determining the outer boundary and the latter determining the inner boundary adjacent to myocardium and coronary vessels[13, 20]. Previously, CCTA and CCS both with ECG-gating were the most commonly used imaging mode in this category[21]. It seemed that heart beat would hinder the measuring procedure. Physiologically, pericardium anchors heart by attaching to sternum, diaphragm and anterior mediastinum[22]. The inelastic characteristics ensures the display of pericardium is not affected by cardiac cycles in non-gated imaging, which was verified in the segmenting step of this study (Figure 1.). With a relatively static of outside boundary, motion of the inner boundary during the cardiac cycle could cause error of EF measurement. However, EFV assessed on diastolic and systolic CCTA reconstructions was not significantly different[23]. The EFV from the systolic and diastolic phase was interchangeable when the other parameters were kept consistent. Without ECG-gating, RCCT hence could be used as an alternative method to assess EF[24-26].

Though there had been abundant reports, the pre-defined thresholds for fat tissue were frequently inconsistent, the lower threshold was usually set at -250HU or -190HU, and the upper at -45HU, -30HU, -15HU[23, 24, 27, 28]. Therefore, it was impossible to compare the results from different studies. Among those, the range of (-190HU, -30HU) was the most commonly used, and we defined the results of this range measured on CCTA as reference. The inconsistency of threshold preserved in the earlier two studies of EFV quantification based non-ECG gated CT comparing with ECG gated cardiac-CT[14, 27]. Simon-Yarza, I. et.al reported the same concordance and reliability between the two approaches using the threshold of (-195HU, -45HU)[27]. And Nagayama, Y et.al found that the EFV measured on non-gated CT

was excellent correlated but approximately 30% higher than that on gated-CT using the threshold of (-190HU, -30HU)[14], which was consistent with our results. This problem hindered the longitudinal observation or retrospective analysis of EF changes unless the same examination conducted every time. However, both CCTA and RCCT had its indications and limitations, the available database would be appreciably expanded if the consistency of EF measurement between them could be improved.

The present study demonstrated that adjusting of the threshold could improve the consistency of EFV from RCCT with that from CCTA. Bucher, A. M et.al systematically analyzed the influence of technical parameters on quantification of EFV at cardiac CT and found that threshold adjustments especially the upper level could make volumetry from different series comparable[23]. Initially, the influence of upper thresholds on the precision of fat volume measurements was reported in 1986 when assessing abdominal fat tissue by CT, and the upper threshold of -30HU which was the mean attenuation difference of body fat and adjacent muscle was used[28]. This definition was used in latter studies regarding EF[23, 28]. Learn from the CT attenuation histogram of EF（Fig.1.c-d.), the frequency near the upper threshold were higher than that near the lower limit about 20 times. Hence the adjustment of the upper limit of the threshold could more affect the number of pixels included and reduce the systematic bias. The latest research shows that peri-coronary fat enhances approximately 4.3HU with iodinated contrast when comparing pre-contrast coronary with postcontrast scanning[30]. These pixels near the upper limit and enhanced in non-contrast images would be excluded when measured in contrasted images when using the same threshold. That's why EFV was overestimated in RCCT, or saying that EFV was underestimated in CCTA.

The EFA was reported as a measures of fat composition which might have influence on the atherosclerotic process[15]. Decreased EFA and increased EFV were associated with higher cardiovascular risk[31]. Furthermore, the latest report suggested that it was EFA, but not EFV, is the independent predictor of obstructive CAD and high-risk plaque[32]. Regrettably, the two studied mentioned above only measured EF in CCS images[14, 27], results after the introduction of the contrast agent were unknown. Most interesting, in the same subjects, the difference of EFA between patients with or without plaque was only detected on non-contrast RCCT, which was not shown on CCTA. This phenomenon suggested the enhancement of EF relating to the metabolic abnormality and inflammation should be kept in mind[18]. As the most promising subsegment of EF, pericoronary fat was found enhanced in the presence of iodinated contrast[30]. Further research should to determine whether the EF in pathological conditions "enhanced" more than that in physiological conditions. However, a bewildering circle existed in screening fatty pixels with attenuation threshold that the threshold would affect the fat volume included and eventually affect the result of mean attenuation when CT was used to assess EF. The solution might be the using functional MRI or positron emission tomography to reveal the composition and functional status of EF[33].

The current study had limitations. Firstly, we did not try to determine the optimal threshold, nor provided a recommended threshold. CT attenuation would vary by equipment manufacturer, performance, and scan parameters. There was no endorsed guidelines to quantify EF currently even we defined EFV measured on

CCTA as reference because it was widely used in previous studies. We proposed the approach of threshold adjusting to reduce the differences of EF measurements between different examination protocols. Secondly, the number of patients was small and the patients with coronary plaque were in early stage and asymptomatic. Predictive efficacy of EF measurements for CAD was not explored.

Conclusions

The present study concluded that RCCT was capable to used assessing EF, and the adjustment of threshold could increase the consistency of EFV measured on CCTA and RCCT. With more and more pathophysiological functions were discovered, this would be useful in some scenarios where there was no need or unsuitable to perform specific cardiac examination. Additionally, EFA assessment may have additional information relating to underlying pathophysiological status.

List Of Abbreviations

CAD: Coronary Artery Disease; CCS: Coronary Calcium Score; CCTA: Coronary CT Angiography; CT: Computed Tomography; ECG: Electrocardiogram; EF: Epicardial Fat; EFA: Epicardial Fat Attenuation; EFV: Epicardial Fat Volume; HU: Hounsfield Unit; LOA: Limits of Agreement; RCCT: Routine Chest CT; SD: Standard Deviation.

Declarations

Ethics approval and consent to participate

This retrospective study performed at one institution was approved by the Institutional Review Board of Zhongshan Hospital of Fudan University. Consent to participate Written informed consent was waived by the Institutional Review Board. We confirm that all methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest to report.

Funding

1. National Natural Science Foundation of China (grant number 91859107)
2. Shanghai Science and Technology Committee (grant number 18DZ1930102)
3. Shanghai Science and Technology Committee (grant number 19411965500)
4. Zhongshan Hospital, Fudan University (grant number 2018ZSLC22)
5. Shanghai Municipal Key Clinical Specialty（grant number W2019-018）
6. Clinical Research Plan of SHDC (grant number SHDC2020CR1029B)
7. Zhongshan Hospital, Fudan University (grant number 2020ZSLC61)

Authors' contributions

LKY contributed to the conception of the study and manuscript preparation; CY and SJX contributed significantly to analysis and manuscript preparation; HD and CY performed the data organization and wrote the manuscript; CY and CWL contributed significantly to data processing; MSZ contributed to the conception of the study and helped perform the analysis with constructive guidance. All authors read and approved the final manuscript.

Acknowledgements

Not applicable

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Tables

Table 1. Patient characteristics and results of EF measurements

	Total	Plaque(+)	Plaque(-)	*P* value
N	83	34	49	
Age	55.3±7.6	57.0±9.0	54.2±6.4	0.097
BMI	24.5±2.9	24.9±2.9	24.1±2.8	0.221
Gender (Male)	46(55.4%	22(64.7%	24(49.0%	0.156*
Hypertension (Yes)	41(49.4%	24(70.6%	17(34.7%	0.001*
Diabetes mellitus (Yes)	42(50.6%	20(58.8%	22(44.9%	0.212
Dyslipidemia (Yes)	37(44.6%	19(55.9%	18(36.7%	0.084
Calcified plaque	\	24(70.6)	\	
Non-calcified plaque	\	10(29.4)	\	
EFV	99.8±37.9	115.6±44.1	88.9±28.6	0.003*
EFV_{N30}	115±41.8	131.2±49.6	103.7±31.2	0.008*
EFV_{N40}	103.1±39.9	118.8±47.6	92.2±29.4	0.006*
EFV_{N45}	98±38.9	112.9±46.6	87.6±28.6	0.009*
EFA	-78.8±4.1	-79.5±3.8	-78.3±4.2	0.204
EFA_{N30}	-78.8±4.3	-80±4.4	-78±4	0.030*
EFA_{N40}	-84±3.6	-84.8±3.9	-83.4±3.3	0.092
EFA_{N45}	-86.2±3.3	-87±3.5	-85.7±3	0.075

Data are shown as mean ± SD or number (%); EFA: Epicardial Fat Attenuation; EFV: Epicardial Fat Volume; Threshold of N30: (-190HU, -30HU), N40: (-190HU, -40HU); N45: (-190HU, -45HU).

Figures

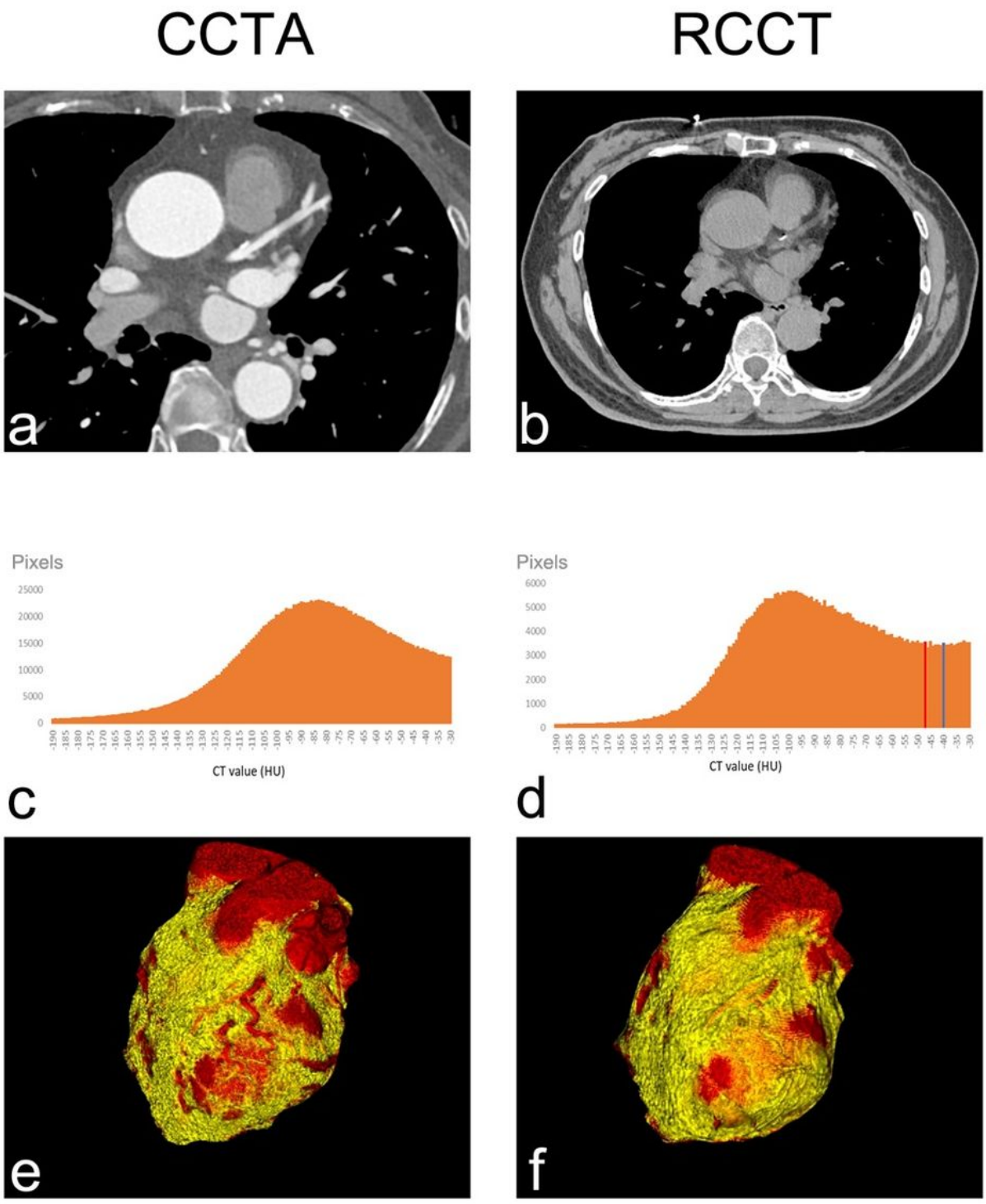

Figure 1

Visualization of EF in axial image, histogram and volume rendering. The pericardial structure (White arrow head) in RCCT could be identified as clearly as CCTA (a-b). The similar pattern of CT value histogram extracted from pericardium segmentation on CCTA and RCCT both indicate the adjustment of upper thresholds had more obvious influence on the precision of fat volume measurements(c-d). The blue

and red line in indicating the CT attenuation of -40HU (N40) and -45HU (N45). Volume rendering of EF and heart were displayed using the same threshold of (-190HU, -30HU). (e-f).

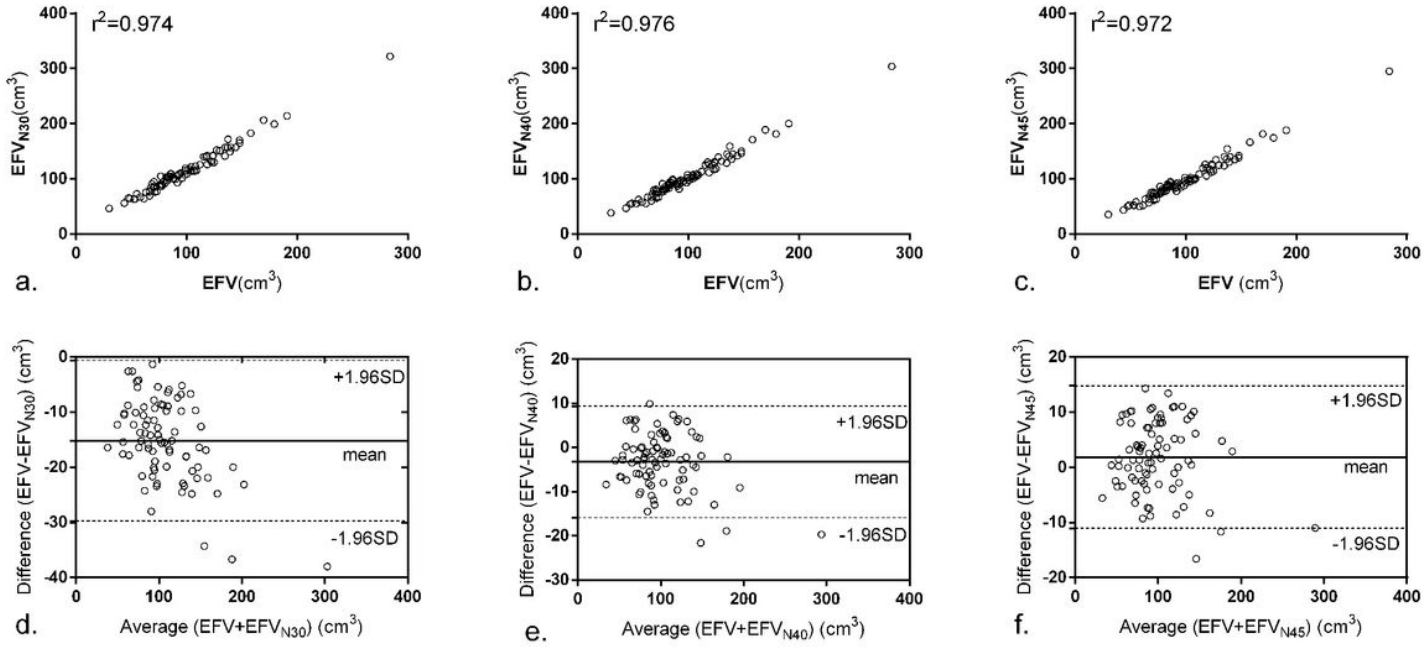

Figure 2

Correlation (a-c) and Bland-Altman plot (d-f) for EFV between CCTA and RCCT using three thresholds. Mean EFV [cm3] is plotted against the relative difference of both measurements. Both dotted lines represent the 95% confidence intervals. Threshold of fatty attenuation: N30 (-190HU, -30HU), N40 (-190HU, -40HU), N40 (-190HU, -45HU).

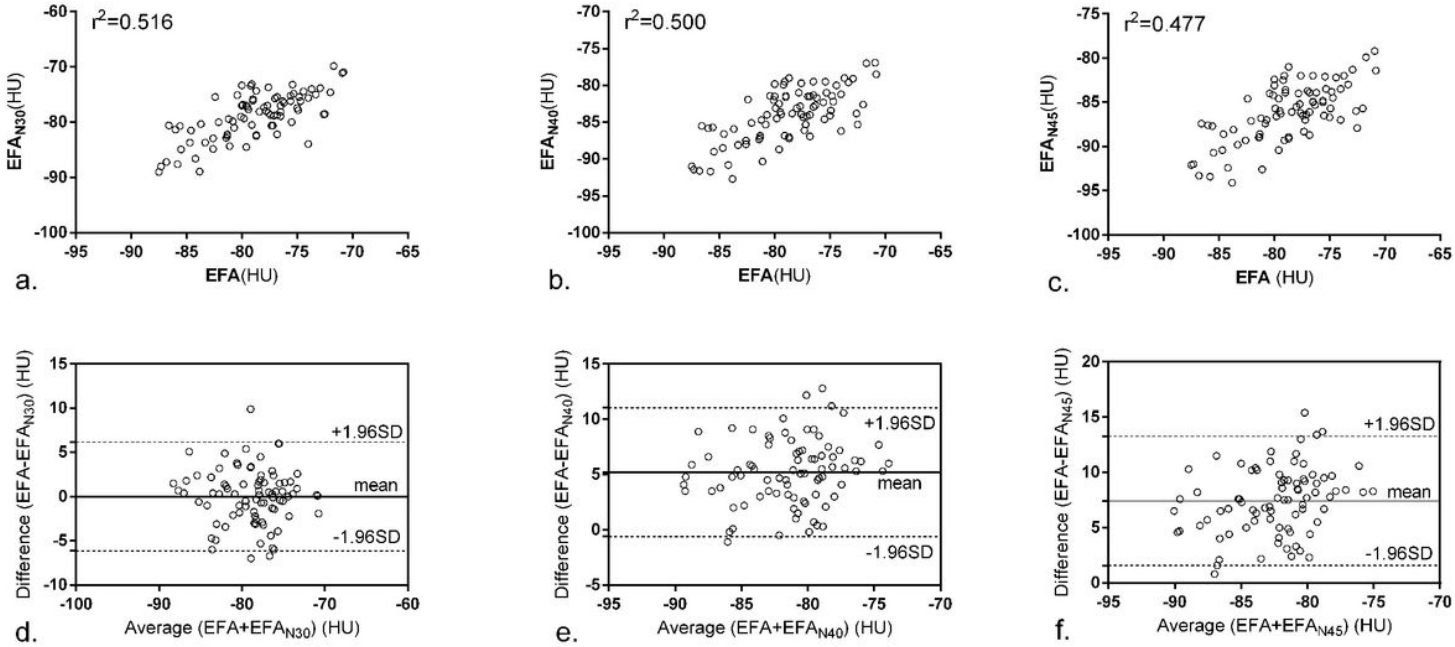

Figure 3

Correlation (a-c) and Bland-Altman plot (d-f) for EFA between CCTA and RCCT using three thresholds. Mean EFA [HU] is plotted against the relative difference of both measurements. Both dotted lines represent the 95% confidence intervals. Threshold of fatty attenuation: N30 (-190HU, -30HU), N40 (-190HU, -40HU), N40 (-190HU, -45HU).

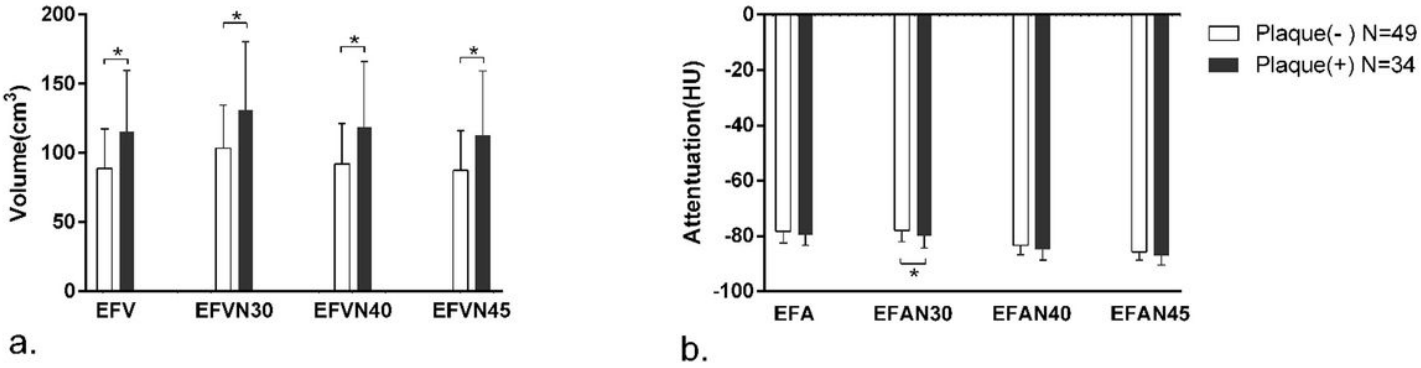

Figure 4

Comparison of EF measurements between the patients with and without coronary plaques. Data measured on CCTA and RCCT both demonstrated the significantly larger EFV of Plaque (+) group than Plaque (-) group (a). The significantly difference of EFA was only shown on RCCT using N30 (b).