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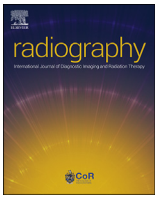

Quantification of epi- and pericardial adipose tissue deposits between males and females during cardiac CT may potentially help categorize coronary artery disease risk with thoracic circumference

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ABSTRACT

Introduction: This study aims to investigate the association between epi- and pericardial adipose tissue deposits around the heart against patient body habitus when using cardiac computed tomography (CT).
Methods: Ninety-two consecutive patients with suspected coronary artery disease underwent coronary CT angiography with quantitative cardiac and adipose tissue volume measurements. Body mass index (BMI), body surface area (BSA), thoracic circumference, anteroposterior diameter, cardiac and adipose tissue volumes were compared between genders by employing Pearson's correlation and results were considered statistically significant if $p \leq 0.05$.
Results: Statistically significant differences between genders were observed with males having a greater height (males 1.72 ± 0.11), BMI (30.76 ± 7.87 kg/m^2), BSA (2.06 ± 0.21 m^2), thoracic circumference (1022.12 ± 97.90 mm^2), and pericardial adipose tissue volume (46.72 ± 36.62 mm^3) ($p < 0.05$). For men, for Group 1 (BMI $\leq$ 27) each of the measured volumes showed moderate correlation between pericardial adipose tissue and AP chest-diameter ($r = 0.429$, $p < 0.05$), whereas in Group 2 (27 < BMI $\leq$ 31.1), coronary artery volume had a strong association with the AP chest-diameter ($r = 0.453$, $p < 0.05$).
Conclusion: BMI and thoracic circumference are closely related to variable epi- and pericardial adipose tissue volumes in both males and females during cardiac CT.
Implications for practice: Quantification of epi- and pericardial adipose tissue deposits between males and females during cardiac CT may help further categorise coronary artery disease risk when including BMI and thoracic circumference for males and females.

Introduction

Obesity is a well-known cardiovascular risk factor, traditionally defined as a body mass index (BMI) > 30 kg/m^2, [1][1] which is susceptible to metabolic abnormalities and cardiovascular disease. It has become evident that the anatomical distribution of adipose tissue is crucial for the biological implications of obesity. Distinctively, adipose tissue deposits surrounding the heart vary and their association with cardiovascular disease are well known.

Pericardial adipose tissue (PAT) is the cardiac visceral fat that is deposited around the coronary arteries.[2] Epicardial adipose tissue (EAT) on the other hand is the fat between the surface of the heart and the visceral layer of the pericardium.[3] The volume of EAT and PAT accounts for 20% and 50% of the cardiac mass, respectively.[4] Several imaging modalities have assessed EAT and PAT, however, cardiac computed tomography angiography (CCTA) provides a greater spatial resolution of the heart, which results in accurate quantification of adipose tissue densities and volumes.[5] EAT and PAT are emerging as a serious contender in risk factor analysis in patients with coronary atherosclerosis.[6,7] PAT, as is with abdominal visceral fat, is a rich source of biologic adipocytokines, which play an important role in the development of atherosclerotic disease and cardiovascular events.[2] Thus, this study aims to investigate the association between EAT and PAT deposits around the heart

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between males and females during cardiac CTA and compare them to multiple potential metabolic risk factors.

Materials and methods

Study population

The Institutional Review Board approved this retrospective study and informed consent was waived. Patients ($n = 92$) suspected of coronary artery disease were referred to the radiology department for a ECG-gated CCTA. All patients were scanned in 2014 and then followed up for 5 years after the study to determine if there were any major adverse cardiovascular events. Heart rate was also collected from the patient's charts documented by the Radiology Nurse at the time of the study.

CCTA scanning protocol and reconstruction

CCTA was performed using a 256-channel computed tomography scanner (Philips Brilliance iCT, Philips Healthcare, The Netherlands). Patients were positioned supine with arms resting on the gantry above the head. An anterior scout was performed, with coverage from the apices (2 cm above the 1st rib) to the diaphragm (2 cm below the lowest costophrenic recess). The CTCA scan range was from the carina to 2 cm below the cardiac apex.

CT scan parameters employed were: detector width of 256 × 0.625 mm, pitch of 0.2:1 ratio, rotation time of 0.27 s, 120 kVp, 140 mA, with x, y, and z-axis modulation (DoseRight), craniocaudal scan direction, and model-based iterative reconstruction (IMR2). Dose reduction strategies were used when feasible, and the phase with the least amount of coronary artery motion was chosen for analysis. Images were reconstructed at 0.625 mm-thick sections.

Contrast media administration

The arrival time of contrast media for each patient was determined by a test bolus at the level of the aortic annulus, and 65–90 mL of iodinated contrast media (Optiray 350 mg/mL, Guerbet, France) material were administered during cardiac CT. The timing of contrast media administration was chosen to optimize uniform contrast enhancement of the coronary arteries at the level of the aortic annulus in the ascending aorta.

Cardiac chambers, coronary arteries, peri- and epicardial adipose volume measurements

Technical inclusion criteria ensuring correct scan range and anatomical inclusion of the origin, pathway, and termination of the cardiac structures, epi- and pericardial adipose were applied to all cases by an expert medical imaging scientist (not included in the study proper). Volume and mass measurements were automatically calculated employing a threshold technique set by the advanced post-processing software workstation (Intellispace, Philips Healthcare, Netherlands), and data were recorded accordingly (Fig. 1). A density range between −190 HU and −30 HU was employed and the selected volume was visually reviewed with multiplanar reconstructions and manual editing to determine the location of EAT and PAT. Additionally, peri- and epicardial adipose volumes were measured and the Hounsfield unit (HU) density for each of the adipose structures was recorded. All measurements were performed using a primary reporting GSDF-calibrated 3-megapixel monitor.

Radiological review

The multi-reader analysis consisted of two cardiothoracic radiologists certified by the American Board of Radiology and The Royal College of Radiologists with a mean of 17 years' experience. Readers were permitted to manipulate the window and level of the images. Each cardiothoracic radiologist reviewed and re-calculated the EAT and PAT volumes on a separate workstation and at separate time intervals.

Statistical analysis

Analyses were conducted using SPSS 24 for Windows (SPSS Inc, Chicago, IL). Results were considered statistically significant if $p \leq 0.05$. Categorical variables are presented as frequencies with percentages, and continuous variables are presented as means ± standard deviations. Patients were divided into two groups between males and females. Using the bivariate Pearson correlation, the Body Surface Area (BSA), thoracic circumference (TC), anteroposterior diameter (AP), and transverse diameters were correlated to the coronary and left ventricular volumes, total adipose surrounding the heart which was then further divided into EAT and PAT. Within each gender, patients were divided into three categories based on their BMI: Group 1: BMI ≤ 27; Group 2: $27 < \text{BMI} \leq 31.1$ and Group 3: BMI >31.1 kg/m^2.[8] Finally, we employed a Shapiro Wilk test to determine data normality.

Results

Patient demographic

The number of males to females in each group (males $n = 49$ and females $n = 43$) were closely matched with no statistical significance ($p > 0.05$). In this study population, there were statistically significant differences between males 1.72 ± 0.11 m, 1022.12 ± 97.90 mm^2, 30.76 ± 7.87 kg/m^2, 2.06 ± 0.21 m^2, and 46.72 ± 36.62 mm^3 respectively) and females (1.63 ± 0.06, 955.47 ± 84.50 mm^2, 29.18 ± 4.84 kg/m^2, 1.88 ± 0.17 m^2 and 31.62 ± 13.10 mm^3 respectively, with the former having greater height, TC, BMI, BSA, and pericardial adipose tissue volumes ($p < 0.05$). Interestingly, there was no significant difference in body weight, total EAT volumes, as well as the density of both EAT and PAT volumes between males and females (Table 1).

Cardiac chambers and coronary volumes, myocardial and left ventricular mass, and heart rate

Further analysis was performed when comparing males and females for each of the volumes measured. The former demonstrates significantly higher measurements in all volumes except for the ascending aortic volume, left atrium, and heart rate (Table 2). Nevertheless, heart rate variation between each group allowed us to further stratify between each gender since the volume of blood does not differ based on the cardiac contraction in the end-diastolic phase in which the heart cycle was captured during imaging.

Correlation between BMI and coronary, cardiac and adipose volumes

The further gender-stratified analysis showed a strong correlation between BSA and left ventricular volume in males. Similarly, TC, AP, and transverse chest-diameter were strongly correlated in the male group with the volumes of total and both EAT and PAT. Additionally, in the female group, there was a strong relationship between total adipose and epicardial tissue volumes and AP chest-

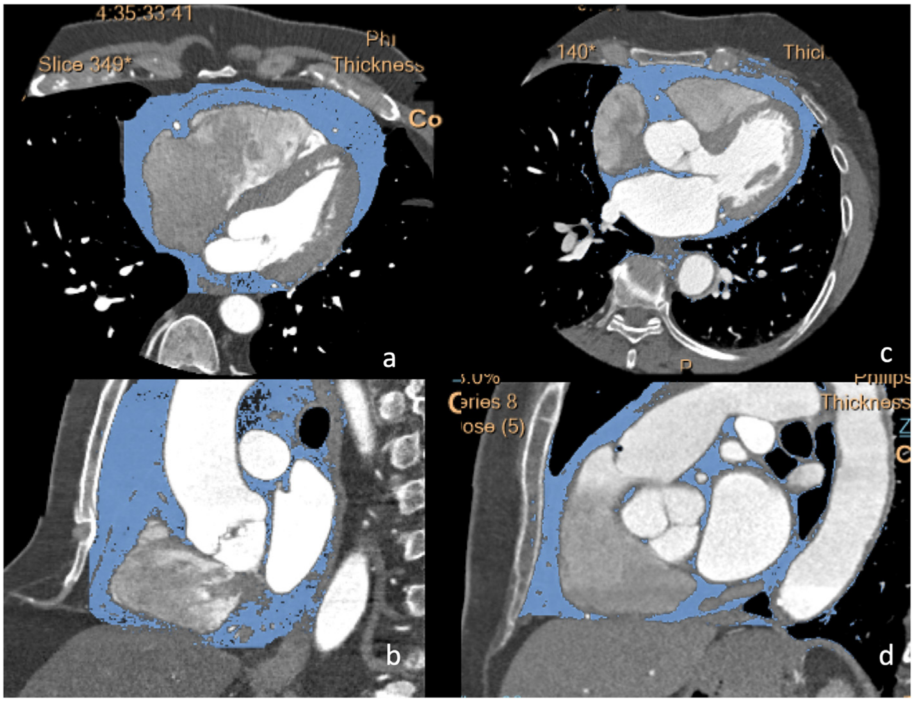

Figure 1. Semi-automated epi and pericardial fat segmentation. Image (a–b) 79-year-old female and image (c–d) 69-year-old male patients with total extra-cardiac adipose tissue segmentation.

Table 1
Patient demographics.

	Female	Male	*p*
Number	43	49	*ns*
Age (y)	54.9 ± 10.5	51.4 ± 10.2	0.111
Height (m)	1.6 ± 0.1	1.7 ± 0.1	0.005
BMI (kg/m^2)	29.1 ± 4.8	30.7 ± 7.8	0.606
Weight (kg)	78.1 ± 13.3	89.7 ± 17.6	0.833
BSA (m^2)	1.8 ± 0.1	2.6 ± 0.2	0.011
Thoracic Circumference (mm)	955.4 ± 84.5	1022.1 ± 97.9	0.032
Anterio-posterior Diameter (mm)	231.2 ± 29.4	249.9 ± 26.9	0.016
Transverse Diameter (mm)	361.6 ± 34.9	385.5 ± 40.2	0.007
Total Cardiac Adipose (mm^3)	141.4 ± 57.4	184.3 ± 103.9	0.181
Pericardial Adipose (mm^3)	31.6 ± 13.1	46.7 ± 36.6	0.045
Epicardial Adipose (mm^3)	109.8 ± 51.9	137.5 ± 78.7	0.254
Pericardial Adipose Density (HU)	89.4 ± 4.6	101.9 ± 94.1	0.160
Epicardial Adipose Density (HU)	88.9 ± 5.1	89.2 ± 4.9	0.605

Table 2
Coronary and cardiac demographics.

Volume (mm^3)	Female	Male	*P*-value
Coronary Artery	30.1 ± 11.7	40.2 ± 15.2	0.001
Ascending Aorta	55.9 ± 22.5	68.1 ± 39.7	0.289
Left Ventricle	115.0 ± 22.3	137.8 ± 26.9	0.001
Left Atrium	78.5 ± 26.2	84.0 ± 18.8	0.062
Myocardial Mass (g/m^2)	95.7 ± 17.6	142.1 ± 33.5	0.001
Right Ventricle	122.2 ± 25.3	162.4 ± 28.4	0.001
Right Atrium	79.4 ± 16.1	90.6 ± 21.2	0.015
Left Ventricular Mass (g/m^2)	100.5 ± 18.5	149.3 ± 35.1	0.001
Heart Rate (bpm)	63.1 ± 7.8	63.8 ± 7.3	0.716

Note: Data are mean ± standard deviation.

diameter ($p < 0.05$) (Table 3). Interestingly, BSA, TC, AP, and transverse chest diameters were not significantly correlated with coronary artery volume in either group. However, there was a positive correlation between AP diameter and epicardial adipose tissue volume around the heart in both groups (male: $r = 0.358$ and female: $r = 0.490$, $p < 0.01$).

Further stratification in each gender was carried out to determine if there were correlations between volumes of the coronary artery, left ventricle, and adipose tissue surrounding the heart. Further subdivision between each group was carried out to determine if there were a correlation between weight groups and these mentioned volumes. Group 1 (BMI<27 kg/m^2) demonstrated a strong correlation between coronary artery volume and BSA ($r = 0.883$, $p < 0.05$), whereas in the male population in the same weight group there was no correlation. In Group 2 ($27 < \text{BMI} \leq 31.1$ kg/m^2) there was a positive correlation between EAT volume and the AP chest-diameter ($r = 0.804$, $p < 0.05$). Whilst in Group 3 (BMI>31.1 kg/m^2), there was no statistical significance in any of the measured volumes (Table 4).

In the male population, when stratifying the weight groups between each of the measured volumes in Table 4, there was moderate correlation and statistical significance in Group 1 between pericardial adipose tissue and AP chest-diameter ($r = 0.429$, $p < 0.05$), whereas in Group 2, coronary artery volume had a strong association with the AP chest-diameter ($r = 0.453$, $p < 0.05$).

Patient clinical follow-up

Of all the patients in this study (92 participants), only 20 patients demonstrated coronary artery disease on calcium score and successive calcium score scans. As such, there were no deaths reported with a 5 year follow up.

Discussion

The current study investigated the quantification of EAT and PAT volumes obtained from cardiac CT, which was later correlated with patient characteristics. Similar to what previous studies have demonstrated, males had larger BMI, height, BSA, TC, and PAT

Table 3
Correlation among males and females when compared to various volumetric constituents.

Volume (mm^3)	BSA		Thoracic Circumference		Anterior-posterior Diameter		Transverse Diameter	
	Male	Female	Male	Female	Male	Female	Male	Female
Coronary Artery	0.059	0.199	0.097	0.247	0.022	0.237	0.116	−0.077
Left Ventricle	0.241^a	0.416	0.105	0.318	−0.008	0.188	0.145	0.309
Total Adipose	0.398^b	0.034	0.363^b	0.115	0.382^b	0.526^a	0.302^b	−0.135
Epicardial Adipose	0.405^b	0.068	0.344^b	0.124	0.358^b	0.490^a	0.288^a	−0.104
Pericardial Adipose	0.260^a	−0.121	0.289^a	0.012	0.315^b	0.365	0.237^a	−0.180

Statistical significance (a): $p < 0.05$ and (b): $p < 0.01$.

Table 4
Correlation-based gender stratification when comparing each BMI group.

Volume (mm^3)	BSA			Thoracic Circumference			Antero-posterior Diameter			Transverse Diameter		
	Grp 1	Grp 2	Grp 3	Grp 1	Grp 2	Grp 3	Grp 1	Grp 2	Grp 3	Grp 1	Grp 2	Grp 3
Females												
Coronary Artery	0.883^a	0.452	0.189	−0.105	0.309	−0.031	0.432	0.139	−0.318	−0.485	0.251	0.115
Left Ventricle	0.312	0.517	0.390	−0.492	0.511	0.478	0.188	0.238	0.240	−0.746	0.414	0.571
Total Adipose	0.695	0.508	−0.151	0.242	0.145	0.059	0.554	0.887^b	0.393	−0.119	−0.161	−0.110
Epicardial Adipose	0.705	0.591	−0.055	0.276	0.245	0.044	0.625	0.804^a	0.355	−0.130	−0.036	−0.114
Pericardial Adipose	0.491	−0.132	−0.588	0.077	−0.281	0.102	0.196	0.493	0.355	−0.057	0.493	−0.026
Males												
Coronary Artery	−0.290	0.201	0.256	0.141	0.307	−0.022	0.020	0.453^a	−0.228	0.159	0.204	0.087
Left Ventricle	0.237	0.061	0.229	−0.193	−0.097	−0.104	−0.071	−0.159	−0.104	−0.204	−0.056	0.399
Total Adipose	0.090	0.366	0.174	0.255	0.284	−0.014	0.376	0.369	0.003	0.132	0.208	−0.021
Epicardial Adipose	0.109	0.349	0.223	0.245	0.293	−0.097	0.307	0.366	−0.043	0.152	0.220	−0.108
Pericardial Adipose	0.016	0.310	0.056	0.201	0.145	0.107	0.429^a	0.251	0.065	0.042	0.081	0.106

Note: groups are denoted as group 1: BMI ≤ 27; group 2: 27 < BMI ≤ 31.1 and group 3: BMI > 31.1 kg/m2. Statistical significance (a): $p < 0.05$ and (b): $p < 0.01$.

volumes, whereas, females had lower PAT volumes, all of which were consistent in our study cohort.[9] EAT was not significantly different between males and females, which was previously reported to be higher in men, but when adjusted to BMI, EAT is comparable in both genders.[10] Moreover, TC was significantly higher in males with increased PAT volumes as compared to females.

The embryonic origins of EAT and PAT differ, with the former originating from the brown adipose tissue while the latter originating from primitive thoracic mesenchyme.[3,7,8] Under normal physiologic conditions, epicardial fat is known to have the following functions: as a buffer, absorbing fatty acids and protecting the heart against high fatty acids levels; as a local energy source at times of high demand, channeling fatty acids to the myocardium; and perhaps as brown fat to defend the myocardium against hypothermia.[8–11] As such, epicardial fat may release factors that blunt the toxic effects of high fatty acid levels on the myocardium and may release factors that promote harmful coronary artery disease and myocardial changes. Nevertheless, it is also known to be a source of proinflammatory and proatherogenic cytokines as well as, produces anti-inflammatory, antiatherogenic adipokines, such as adiponectin and adrenomedullin.[8–11] Epicardial fat has shown a strong direct correlation with obesity and general body adiposity.[12–14]

A study performed by Sales et al. demonstrated that TC can be a newly identified potential risk factor for cardiovascular disease.[15] Besides, coronary artery calcium (CAC) has been widely used as a prognostic tool in asymptomatic patients for risk stratification where an increased CAC is associated with a higher mortality rate regardless of gender, age, or ethnicity.[16–19] Finally, EAT demonstrated a relationship between EAT volume and coronary artery disease, with the presence and progression of coronary plaque burden as measured by the coronary calcium score.

High TC values are strongly associated with metabolic syndrome in patients with CVD. With TC becoming an emerging risk factor,[15] EAT, on the other hand, has been well associated with CVD.[20] This association further supports the role of TC in CVD and the gap in the literature between TC and EAT. Similarly, EAT volumes are reported to be higher in men than in women, however, when our data was adjusted for BMI, EAT volume/BMI, males and females had comparable volumes with no statistical significance. This in itself affects CAD.[10] Interestingly, in our study, we found that TC was strongly correlated with EAT in females in the BMI range greater than 31.1 kg/m^2 than males. Therefore, whilst there is a correlation between females and not males in the larger BMI group, further stratification is recommended to determine whether TC is a potential risk factor for CVD.

During CCTA, females usually have a lower PAT volume than men of all ages. PAT volume increases with age and in one study was found to increase from 148 ± 77 cm^3 in patients less than 40 years old to 252 ± 118 cm^3 in patients above 70 years old.[9] In our study, PAT volumes were stratified according to BMI, males with a BMI of less than 27 kg/m^2 had a strong correlation between PAT volumes and AP diameter. Currently, there is no description of such a relationship in literature. Nevertheless, in this BMI group, females showed a strong correlation between BSA and coronary artery volumes. Cantor et al. demonstrated a poor correlation between BSA and coronary vessel size measured as diameter, but no published studies tackled volumetric measurements as well as risk analysis.[21] Finally, PAT volume is significantly associated with coronary plaque and coronary volumes, especially the left circumflex coronary artery. As such, PAT has become an important biomarker for CVD risk assessment.[22] In our study, we did not correlate plaque burden on EAT or PAT volumes, since not all patients in this cohort did not have a positive calcium score, thus, limiting statistical significance between males and females.

We identified several limitations in our study. Measurements in this study of PAT and EAT volumes were not verified by a gold standard like biopsy which would histopathologically prove the tissue being measured. However, the quantification and identification method used has proven high accuracy. Moreover, EAT and PAT volumes were not cross-referenced with MRI volumes as well as cadaver analysis. Patients enrolled have presented with chest pain and thus results might not apply to other clinical settings. Finally, further studies are needed to obtain a clearer image of the confounders and true risk factors for cardiovascular disease. The patient follow-up did not occur beyond 5 years to determine whether these studied factors had any impact on mortality. Finally, the correlation between EAT and PAT volumes were not correlated to coronary plaque burden due to limited numbers that had calcium deposits.

Quantification of epi- and pericardial adipose tissue deposits between males and females during cardiac CT may help further categorise coronary artery disease risk with BMI and TC between males and females. Further investigations on patient outcomes are required along with risk factor collection and stratification for better prediction and association models.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee.

Informed consent

Informed consent was waived as this was a retrospective study

Conflict of interest statement

None.

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