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ORIGINAL ARTICLE

The correlation of epicardial adipose tissue on postmortem CT with coronary artery stenosis as determined by autopsy

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Abstract The goal of this study was to assess whether epicardial and paracardial adipose tissue volumes, as determined by computed tomography (CT), correlate with coronary artery stenosis as determined by autopsy. The postmortem CT data and autopsy findings of 116 adult human decedents were retrospectively compared. Subjects were classified into three groups according to their degree of coronary artery stenosis: ≥50, <50 %, and no stenosis. Epicardial and paracardial adipose tissue volumes were calculated based on manual segmentation after threshold based masking. In addition, epicardial adipose tissue thickness was measured using a caliper. All three parameters (thickness of epicardial fat and volumes of both epicardial and paracardial fat) were compared among the three groups and correlated with the degree of coronary artery stenosis. The group with no coronary artery stenosis showed the lowest mean values of epicardial adipose tissue volume, while the coronary artery stenosis ≥50 % group showed the highest volume. All measured variables (thickness of epicardial fat and volumes of both epicardial and paracardial fat) correlated significantly with the grade of coronary artery stenosis, even after controlling for BMI, however, epicardial adipose tissue volume exhibited the strongest correlation. This study reveals that there is an association between the degree of coronary artery stenosis and the amount of epicardial fat tissue: The larger the volume of epicardial fat, the higher the degree of coronary artery stenosis.

Keywords Epicardial adipose tissue · Coronary artery stenosis · Postmortem imaging · Postmortem CT · Virtopsy

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Introduction

Epicardial adipose tissue is defined as a visceral fat deposit, located between the outer wall of the myocardium and the visceral layer of the pericardium [1]. This lipid storage secretes inflammatory factors such as adipokines and pro-inflammatory cytokines, which may favor the development of atherosclerosis [2]. Both the epicardial adipose tissue and the coronary artery wall share a common blood supply [1]. Hence, this aspect may play a role in the pathogenesis of coronary artery disease [2–4].

Paracardial adipose tissue is identified as a fat deposit situated on the outer surface of the parietal layer of the pericardium and within the mediastinum [2]. Paracardial fat also receives its blood supply from a different source, namely a branch of the internal mammary artery, the pericardiacophrenic artery [2]. Pericardial fat is defined as epicardial fat plus paracardial fat [2].

Coronary artery disease in living patients is a clinical diagnosis, which can be visualized using contrast-enhanced cardiac computed tomography (CT), thereby giving information about lesion severity and plaque morphology [5].

This diagnostic tool also allows for accurate and reproducible volume quantification of both epicardial and paracardial adipose tissue [6–10]. Several studies provide strong evidence that the presence and extent of coronary atherosclerosis are associated with the amount of epicardial adipose tissue [11–15]. One study supports the fact that epicardial adipose tissue volume is almost twice as high in patients with high-risk coronary lesions and is significantly associated with high-risk coronary lesion morphology [16]. Recent data indicates that greater epicardial adipose tissue volumes are found in patients with plaques that are not primarily comprised of calcium, as opposed to those consisting mainly of calcium [17–19]. There are studies demonstrating the association of pericardial fat with calcified coronary arteries [20, 21]. It has also been shown, that epicardial fat volume is associated with several cardiovascular risk factors, including hyperglycemia, hypertension, and hypercholesterolemia [22].

Over the past 10 years postmortem CT (PMCT) and postmortem MR (PMMR) have been implemented in forensic medicine as an adjunct or alternative to invasive autopsy [23]. Studies analyzing the findings of virtual autopsies and comparing them to traditional autopsies have shown a high correlation between the two methods [24–30].

Based on a review of the literature, we hypothesized that the amount of epicardial and paracardial adipose tissue correlates to the severity of coronary artery occlusion as identified at autopsy. The goal of this study was to assess if epicardial and paracardial adipose tissue volumes as found by CT correlate to the degree of coronary artery stenosis as determined by autopsy.

Materials and methods

Study design and subjects

The study population was examined at the Institute of Forensic Medicine, University of Zurich, between July 2011 and November 2011. In total, 157 cases were referred for both a whole-body PMCT and an autopsy examination, which were ordered by the local justice department. Of these, 41 were excluded from the study population. Exclusion criteria were: age under 17 years (3 cases), advanced decomposition (31 cases) [31], pericardial tamponade (3 cases), penetrated pericardium (2 cases), explantation (1 case), and no subsequent autopsy (1 case). 1 case did not meet the criterion of the required soft tissue window thoracic reconstruction, however it was not excluded for the 2 dimensional measurements. Thus, of the 116 cases that were included in the study and retrospectively evaluated, 115 were segmented. The study population comprised a total of 70 males and 46 females. The mean age was 55.1 years (range 17–95 years, median 54.0 years).

Imaging protocol

Postmortem imaging was performed on a dual-source CT scanner SOMATOM® Definition Flash (Siemens Medical Solutions, Forchheim, Germany). Imaging parameters were set as recommended by recent literature [32] in the following manner: tube voltage was 120kVp, slice collimation was 128×0.6 mm. All scans were performed using automatic dose modulation software Siemens CARE Dose4D™ (Siemens Medical Solutions, Forchheim, Germany). The PMCT image reconstructions with a slice thickness of 1.0 mm in increments of 0.6 mm, using the soft-tissue kernel, were evaluated.

Assessment of adipose tissue on PMCT

One-dimensional measurements of the epicardial adipose tissue thickness were performed at the coronary sulcus, anterior interventricular sulcus, and posterior interventricular sulcus using a caliper tool. For these measurements a Picture Archiving and Communication System (PACS) workstation IDS7 (Sectra AB, Linköping, Sweden) was used. The PMCT data sets were reviewed in multi-planar reconstructions, after adjusting the planes to a four-chamber and short-axis view of the heart. The epicardial adipose tissue thickness of the coronary sulcus was assessed at the mid-ventricular four-chamber plane, and both the anterior and posterior interventricular sulci measurements were calculated at the proximal one-third of the left ventricle. A mean thickness of the epicardial adipose tissue was then calculated.

For the assessment of the adipose tissue volume, the segmentation software Amira® (Version 5.4.1, Visage Imaging, Inc., Germany) was used. To facilitate segmentation process, the data sets were firstly re-sampled in axial orientation with a slice thickness of 5 mm. The epicardial and paracardial adipose tissue was segmented in a manual manner, using threshold based masking. Voxels corresponding to adipose tissue were identified using threshold attenuation values of -190 to -30 Hounsfield units (HUs) [7, 20, 33]. The region of interest for the segmentation of both epicardial and paracardial adipose tissue were defined proximally at the height of the inferior wall of the aortic arch and ended at the level of the last slice where the pericardial sac was still visible. Initially, tracing of the epicardial adipose tissue on each slice situated between the above-mentioned levels was done manually. Subsequently, and in an analog fashion, the paracardial adipose tissue was then traced. Depending on heart size, the number of manually traced slices varied from approximately 21–30 in each case. Improvement in tracing accuracy when needed was provided by the coronal and sagittal views. Finally, based on the segmentation, the epicardial and paracardial adipose tissue volumes were calculated in ml (Figs. 1 and 2).

The reviewer of the one-dimensional measurements had 5 years experience in PMCT imaging. The reviewer of the epicardial and paracardial fat volumes had a medical background and was trained for the task.

Assessment of coronary artery stenosis at autopsy

The autopsy report was retrospectively evaluated for the degree of coronary artery stenosis, age at death, sex, height, and weight. The body mass index (BMI) was calculated (weight in kilograms divided by the height in meters squared). The degree of coronary artery stenosis was determined by multiple cross-sectional sections of the coronary arteries. The most significant grade of stenosis for each one of the three major coronary arteries branches was recorded in the autopsy protocol. Subjects were classified into three groups according to the degree of coronary artery stenosis: Group 1: stenosis $\geq$50 %, Group 2: stenosis $<$50 %, and Group 3: no stenosis. No clinical classification of significant and insignificant degree of stenosis was used, as it was not within the scope of the study to explore the correlation of the examined variables with cardiac causes of death. The reviewer of the volumetric measurements of the epi- and paracardial fat was blinded to the degree of coronary artery stenosis.

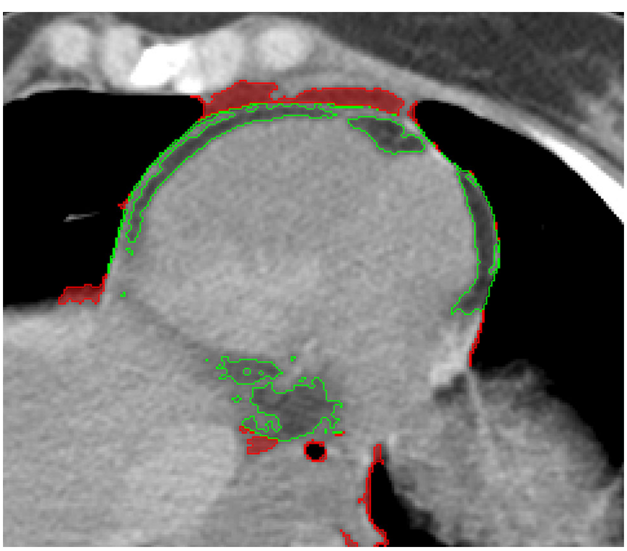

Fig. 1 Axial PMCT at the level of the heart. The epicardial and paracardial adipose tissues are manually segmented and marked with *different colors* (*green*: epicardial tissue, *red*: paracardial tissue)

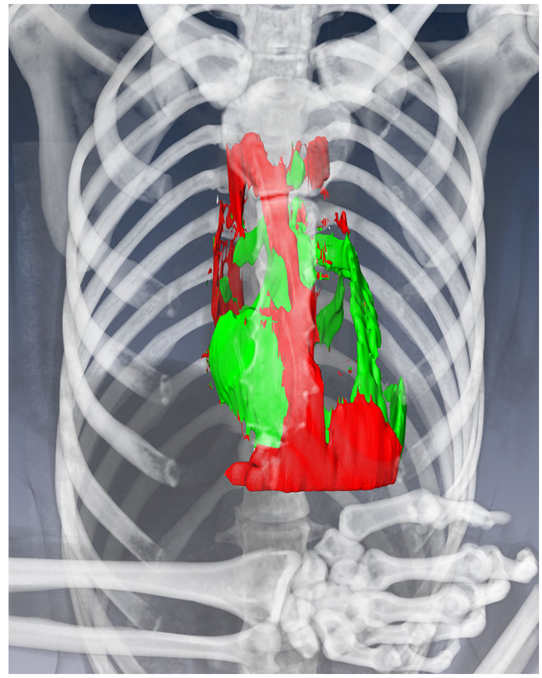

Fig. 2 Three dimensional volume rendering of a segmented case. The epicardial adipose tissue is *colored green* and the paracardial *red*

Statistical analysis

All data analysis was performed using a statistical software package SPSS® (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, USA). Continuous data were summarized as means ± standard deviations, whereas categorical data were presented as absolute numbers. The Shapiro–Wilk test was used to assess the normality of distribution of data. We used the Kruskal–Wallis test to assess whether the mean values for the epicardial adipose tissue mean thicknesses and the epicardial and paracardial adipose tissue volumes were significantly different between the 3 coronary artery stenosis groups. Because of the multiple tests, the Bonferroni adjustment for the critical p value was applied. Statistical significance was determined if $p < 0.017$ (0.05/3). The post hoc test Tukey HSD was carried out in order to determine which groups presented with a statistically significant difference. The correlations between the mean thickness of the epicardial adipose tissue and the epicardial and paracardial adipose tissue volumes were calculated using Spearman's rho correlation test. For testing whether the BMI had an influence on these correlations, a partial correlation test was performed using the BMI as control variable. The results of the one- and three-dimensional measurements were also correlated with the 3 coronary artery stenosis groups using the partial correlation test with the BMI as control variable. A p value of $<$0.05 was considered statistically significant.

Results

Within the study population, 33 subjects presented with no coronary artery stenosis (mean thickness of the epicardial adipose tissue was 11.16 mm, mean epicardial adipose tissue volume was 80.02 ml, and mean paracardial adipose tissue volume was 128.37 ml), 42 with a coronary artery stenosis <50 % (mean thickness of the epicardial adipose tissue was 12.03 mm, mean epicardial adipose tissue volume was 101.94 ml, and mean paracardial adipose tissue volume was 172.36 ml), and 41 with a coronary artery stenosis ≥50 % (mean thickness of the epicardial adipose tissue was 12.93 mm, mean epicardial adipose tissue volume was 120.82 ml, and mean paracardial adipose tissue volume was 173.82 ml). Table 1 summarizes the results of the 3 measured variables. Hence, the 3 measured variables (i.e., mean epicardial adipose tissue thickness, epicardial adipose tissue volume, and paracardial adipose tissue volume) presented the lowest mean values for the no coronary artery stenosis group, and contrarily the highest for the coronary artery stenosis ≥50 % group.

Mean BMI was 25.85 (SD 8.35), 25.16 (SD 4.50), and 24.59 (SD 3.63) for the subject groups presenting with no coronary artery stenosis, with a coronary artery stenosis <50 %, and with a coronary artery stenosis ≥50 %, respectively.

The Shapiro–Wilk test of normality demonstrated that all variables except age were not normally distributed ($p < 0.05$). Therefore, non-parametric tests were applied for statistical analysis. The statistical analysis results are shown in Table 2.

A non-parametric Kruskal–Wallis test and a post hoc test Tukey HSD showed a statistically significant difference between the means of the epicardial adipose tissue volumes, between the no coronary artery stenosis group and the coronary artery stenosis ≥50 % group ($p = 0.009$). All other comparisons were not statistically significant. This was also the case for comparisons consisting of the means of the paracardial adipose tissue volumes and the epicardial adipose tissue thickness.

The Spearman's rho correlation test between the mean epicardial adipose tissue thickness and the epicardial adipose tissue volume and paracardial adipose tissue volume exhibited statistically significant correlations (correlation coefficient 0.646 and 0.480 respectively, $p < 0.0005$ for both). Additionally, both the epicardial and paracardial tissue volumes positively correlated with each other in a statistically significant manner (correlation coefficient 0.742, $p < 0.0005$). Even after considering the possible influence of the BMI as a control variable, the correlations still exist at a statistically significant level.

Significant correlations were also obtained between the mean epicardial adipose tissue thickness, the epicardial and paracardial adipose tissue volumes, and the classification in 3 coronary artery stenosis groups (Group 1: ≥50 %

Table 1 Results of the one-dimensional (thickness) and volume measurements of the epicardial tissue and the volume measurements of the paracardial tissue in the three groups

	No stenosis ($N = 33$)								<50 % ($N = 42$)							
	Thickness (mm)				Volume (ml)				Thickness (mm)				Volume (ml)			
	Mean	Range	SD	Median	Mean	Range	SD	Median	Mean	Range	SD	Median	Mean	Range	SD	Median
Epicardial Adipose Tissue	11.16	6.55–19.84	3.31	11.09	80.02	14.27–280.74	55.05	63.63	12.03	6.83–18.06	2.65	11.89	101.94	30.79–267.92	55.45	85.62
Paracardial Adipose Tissue					128.37	10.14–448.67	113.32	84.20					172.36	22.05–578.16	124.63	152.54

	≥50 % ($N = 41$)							
	Thickness (mm)				Volume (ml)			
	Mean	Range	SD	Median	Mean	Range	SD	Median
Epicardial Adipose Tissue	12.93	8.09–21.30	3.15	12.76	120.82	27.51–352.29	62.04	107.59
Paracardial Adipose Tissue					173.82	47.81–485.48	92.32	153.79

Table 2 A. Significant differences of the measured variables (mean epicardial adipose tissue thickness, epicardial adipose tissue volume, and paracardial adipose tissue volume) between the 3 coronary artery stenosis groups. The Kruskal–Wallis test was used with the Bonferroni correction: critical $p < 0.017$ (0.05/3), the groups with differences were defined with the Tukey HSD post hoc test. None means that there was no difference in the measured values between any groups. B. 1. Correlation between the measured variables (Spearman Rho test), the p value is given in brackets. 2. Partial correlation between measured variables after controlling for BMI (p value is given in brackets). C. Partial correlation of each of the measured variables (mean epicardial adipose tissue thickness, epicardial adipose tissue volume and paracardial adipose tissue volume) and the classification in the 3 coronary artery stenosis groups, after controlling for BMI. (Note that the negative correlation means that the higher the measured variable, the lower the classification rank in the coronary artery stenosis group, so the larger the stenosis)

	Mean epicardial adipose tissue thickness	Epicardial adipose tissue volume	Paracardial adipose tissue volume
A. Significant differences between the 3 coronary artery stenosis groups	No ($p = 0.03$) none	Yes ($p = 0.003$) No stenosis/over 50 % stenosis	No ($p = 0.028$) none
	Mean epicardial adipose tissue thickness/epicardial adipose tissue volume	Mean epicardial adipose tissue thickness/paracardial adipose tissue volume	Epicardial adipose tissue volume/paracardial adipose tissue volume
B. 1. Correlation between measured variables without and	Yes (0.646, $p < 0.0005$)	Yes (0.480, $p < 0.0005$)	Yes (0.742, $p < 0.0005$)
2. After controlling for BMI	Yes (0.535, $p < 0.0005$)	Yes (0.273, $p = 0.003$)	Yes (0.666, $p < 0.0005$)
	Mean epicardial adipose tissue thickness/coronary artery stenosis groups	Epicardial adipose tissue volume/coronary artery stenosis groups	Paracardial adipose tissue volume/coronary artery stenosis groups
C. Partial correlation after controlling for BMI between the measured variables and the coronary artery stenosis groups	Yes (−0.293, $p = 0.002$)	Yes (−0.320, $p = 0.001$)	Yes (−0.234, $p = 0.013$)

stenosis, Group 2: <50 % stenosis, and Group 3: no stenosis) after controlling for the BMI (partial correlation after controlling for BMI between the artery stenosis group classification and: mean epicardial adipose tissue thickness −0.293, $p = 0.02$, epicardial adipose tissue volume −0.320, $p = 0.01$, paracardial adipose tissue volume −0.234, $p = 0.013$). In other words, the higher the epicardial adipose tissue volume, the lower the classification rank, which means, the higher the degree of coronary artery stenosis. This remained valid for the mean epicardial adipose tissue thickness and paracardial adipose tissue volume.

Discussion

The present study demonstrated that between the group with no coronary stenosis and the ≥50 % coronary stenosis group, the epicardial adipose tissue volume presented statistically significant differences. Moreover, epicardial (thickness and volume) and paracardial fat (volume) correlated significantly with the classification into the 3 coronary artery stenosis groups, even after controlling for BMI.

The results of the underlying study are in line with prior studies showing that greater epicardial adipose tissue volume is related to higher coronary artery stenosis [17].

As reported by Xu et al. [15], the epicardial adipose tissue thickness and volume were significantly higher in patients with coronary artery disease. Likewise, patients presenting with coronary plaque also had increased epicardial adipose tissue volume. However, no effect was found from any coronary artery calcium scores. This meta-analysis study relating to living patients concluded epicardial fat might be considered an effective marker in the prediction of coronary artery disease. These findings are similar to those observed in our study. This emphasizes that our results, albeit estimations, seem to be accurate and reproducible.

There are several limitations to this study, which deserve to be mentioned. Firstly, no biochemical or laboratory results were evaluated due to the nature of the study population. Hence, no metabolic aspects involved in coronary artery stenosis were taken into consideration here.

The degree of coronary artery stenosis is subjectively assessed during autopsy and heart dissection. Consequently, this assessment depends on the pathological experience of the examiner. The autopsies were performed by 2 forensic pathologists, of whom at least one was board certified. In this manner bias was minimized, however not eliminated. The study population was divided into three groups according to the degree of coronary artery stenosis. This classification was not based on critical stenosis for cardiac arrest, as the number of cases would not allow for reliable statistical analysis.

With reference to current literature, there are differences in anatomic description (epicardial versus pericardial adipose tissue) and measurement techniques (thickness versus volume determination) in assessing cardiac fat deposits

[11, 34, 35]. Because delimitation of adipose tissue from other surrounding tissue on CT is based on preset threshold attenuation values, the identification of such tissue is at best only an estimate, which according to previous studies is a valid method of measurement.

The purpose of voxel resampling was to enable and expedite the segmentation process. The extent to which this affected the accuracy of virtually estimated adipose tissue volumes was not specifically tested in this study. However, speeding up the segmentation process made downsampling a justifiable decision [27]. Overall, the segmentation process took, on average, 35 min per case, even after voxel resampling and increasing segmentation experience. This should be considered a possible limitation of the method in an acute clinical setting but not in elective examinations. Nevertheless, implementing such a segmentation process within the clinical sphere as a diagnostic tool and thereby providing valuable information may lead to benefits involving preventative measures, which outweigh the disadvantages of this prolonged period of assessment time. Possible improvements to this segmentation process in the future may include employing automated calculation methods, which in turn would deliver immediate volume estimations to the treating physician.

The findings of the present study confirm the results of analogue studies on living study populations. The extended application of radiological methods in forensic institutes all over the world during recent years has led to new research questions that have to be answered. Clinical knowledge cannot be directly transferred to postmortem cases. Confirmation in a forensic setting with proper scientific studies is required first. The extent of applicability of the new gained knowledge on our routine work is unknown in many cases and has to be determined with application studies. However, defining the quantity of epicardial adipose tissue in cases where autopsy is denied could be used as an indicator for the degree of coronary artery stenosis and, furthermore, coronary artery disease.

Conclusion

This study reveals that there is an association between the degree of coronary artery stenosis and the amount of epicardial fatty tissue: the larger the volume of epicardial fat, the higher the degree of coronary artery stenosis.

Keypoints

1. Recent literature suggests that epicardial adipose tissue may play a role in the pathogenesis of coronary artery disease.
2. Two- and three dimensional measurements of the epicardial and three-dimensional measurements of the paracardial adipose tissue were correlated with coronary artery stenosis as determined at autopsy.
3. There is an association between the degree of coronary artery stenosis and the amount of epicardial fat tissue even after controlling for BMI.
4. The larger the volume of epicardial fat, the higher the degree of coronary artery stenosis.

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