Iranian Heart Journal; 2021; 22 (3)

Original Article

Correlation Between Heart Mediastinal and Epicardial Fat Volumes and Coronary Artery Disease Based on Computed Tomography Images

Ali Kazemi[1], MS; Ahmad Keshtkar[1*], PhD; Saeid Rashidi[2], PhD; Naser Aslanabadi[3], MD; Behrouz Khodadad[3], PhD; Mahdad Esmaeili[1], PhD; Elgar Enamzadeh[3], MD

ABSTRACT

Background: Mediastinal and epicardial adipose tissues are correlated with several adverse metabolic effects and cardiovascular diseases, especially coronary artery disease (CAD). The manual measurement of these fat tissues is widely done in clinical practice due to its human efficacy. As a result, the automated measurement of cardiac fats could be considered one of the most important biomarkers for cardiovascular risks in imaging and medical visualization by physicians.

Methods: In this cross-sectional study, 2 non-contrast computed tomography (CT) data sets were used. An algorithm was designed based on data from 20 patients for cardiac fat measurement. One hundred twenty patients were examined to determine the relationship between CAD and the volume of cardiac fats using coronary artery calcium scoring assessment.

Results: In the examination of the correlation between CAD and the volume of cardiac fats, coronary artery stenosis was severe in 11 patients (9.2%), moderate in 15 patients (14.2%), and mild in 17 patients (14.2%); additionally, no coronary artery stenosis was detected in 77 patients (64.2%). Cardiac fat was measured with an accuracy of 99.2%, and the best threshold obtained an epicardial fat volume (EFV) of 140 mL and a mediastinal fat volume (MFV) of 94 mL for having the largest correlation. In addition, with the increment in the severity of CAD, there was a considerable increment in cardiac fat volume and a significant linear correlation between coronary artery stenosis and MFV (r =0.36; P <0.001) and EFV (r =0.322; P <0.001).

Conclusions: Cardiac fat tissues could be utilized as a trustworthy biomarker tool to predict the extent of CAD stenosis. ***(Iranian Heart Journal 2021; 22(3): 53-63)***

KEYWORDS: Computed tomography, Coronary artery disease, Mediastinal fat volume, Epicardial fat volume, Thoracic fat volume

[1] Department of Biomedical Engineering, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, IR Iran.
[2] Faculty of Medical Sciences and Technologies, Science and Research Branch, Islamic Azad University, Tehran, IR Iran.
[3] Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, IR Iran.

***Corresponding Author:** Ahmad Keshtkar, PhD; Department of Biomedical Engineering, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, IR Iran.
Email: mpp98ak@gmail.com **Tel:** +989123614305

Received: April 17, 2020 **Accepted:** August 18, 2020

The fats around the internal organs as visceral adipose tissues may be a marker for the increased risks of different cardiovascular and metabolic diseases. Mediastinal (also known as pericardial fat) and epicardial visceral fat tissues of the heart are associated with various adverse metabolic effects and cardiovascular risk factors. [1–4] Epicardial fat tissue (EFT) is placed within the pericardium visceral sac (around the heart) and mainly within the interventricular and atrioventricular grooves, along the main coronary artery branches. It is slightly focused on the left ventricular apex, over the free wall of the right ventricle (RV) and around the atria. Mediastinal fat tissue (MFT) is also situated on the fibrous outer surface of the pericardium within the mediastinum area. [5] The pericardium layer separates these 2 fats (Fig. 1).

Recent studies have shown that MFT and EFT have high predictability because of adjacency to the heart and the outer cover of the coronary artery. [6] Sicari et al [7] showed that more mediastinal fat than epicardial fat could indicate risks of cardiovascular diseases. Given the importance of mediastinal and epicardial fat and their correlation with various metabolic and cardiovascular diseases, the measurement of cardiac fats is the foremost critical issue in the analysis of cardiological images. Computed tomography (CT) images provide the most exact measurement of fat tissues during a comprehensive assessment of the heart and the coronary artery structure because of their utilization in the assessment of coronary artery calcium (CAC) scoring and coronary artery disease (CAD), [8] as well as the creation of higher spatial and temporal resolution than echocardiography and magnetic resonance imaging. [9, 10] What necessitates the design of an algorithm for the automated evaluation of fat tissues is the plethora of available data, as well as disagreements between observers, the inadequacy of manual segmentation by technicians, and extra costs.

METHODS

Participants

In this study, 2 data sets of CT images were used. The first data set was utilized for the cardiac fat measurement and the design of an algorithm. [11] The database of cardiac CT scans featured 878 slices of 20 patients, in whom cardiac fats were manually divided by a computer operator under the guidance of a physician. The second data set was utilized to investigate the relationship between CAD and the volume of cardiac fats. Between June 2017 and January 2019, 120 adult patients undergoing non-contrast multi-slice CT with suspected CAD were assessed. This data set featured CT images of 120 patients diagnosed with CAD based on CAC scoring by a cardiovascular specialist and radiologist. Of this total, 43 patients had CAD, and the rest of the subjects were categorized in the healthy group. This data set was collected from the Parsian CT Angiography Medical Center in Shahid Madani Hospital, Tabriz. Finally, after the segmentation of the images using the designed algorithm, the volumes of mediastinal and epicardial fats of the heart were calculated to evaluate their association with CAD.

CAC Scoring

The findings of CAC in heart CT are deemed a reliable and strong marker of coronary artery atherosclerosis. CAC represents one-fifth of the total plaque burden, indicating a high linear correlation with the second root of total pathologic plaque levels (r = 0.90; P <0.001). CAC may be a more sensitive and specific

determinant of CAD risk than conventional CAD risk factors, which may indicate over- and under-diagnosis in arterial atherosclerosis. CAC scanning is a non-contrast-enhanced image acquisition technique that is performed while holding the breath. The weighted sum of CAC is defined by areas in the coronary artery with Hounsfield unit values greater than 130 including 3 or more adjacent pixels. Standard CAC classifications based on studies generally agree that CAC values of 0 to 10 indicate no calcified plaque, and values of 11 to 100, 101 to 400, and more than 400 indicate mild, moderate, and severe CAC levels, respectively. [12]

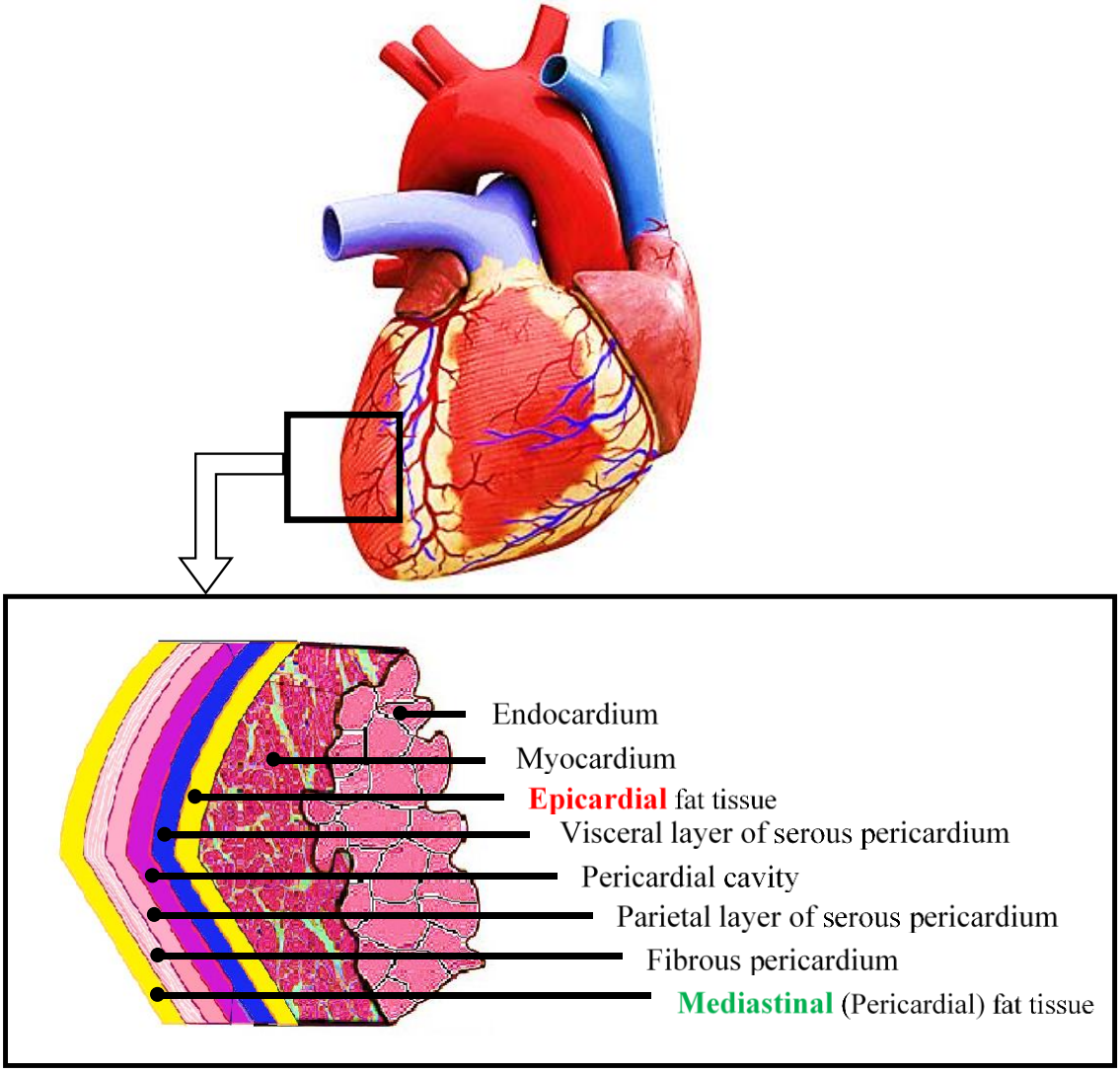

Figure 1. The images depict the position of mediastinal and epicardial visceral adipose tissues around the heart.

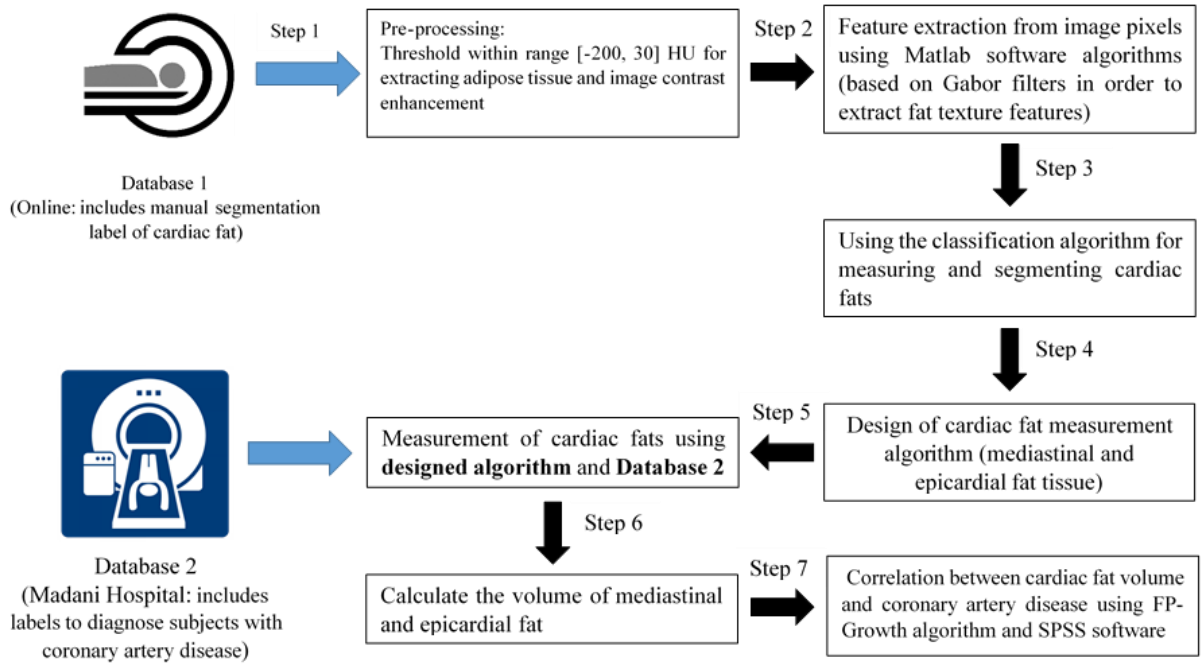

Figure 2. Steps for the designed algorithm to correlate the volume of cardiac fat with coronary artery disease are illustrated herein.

Mediastinal and Epicardial Adipose Tissue Volume Measurements

The steps of the designed algorithm to measure cardiac fat volume and association with CAD are shown in Figure 2. To acquire cardiac fat tissue and remove anatomical structures related to the ribs, the sternum, the diaphragm, the liver, and the lungs in cardiac CT images, we need to determine a range near −100 HU (related to the whole-body fat). We utilized an easy threshold to obtain adipose tissue in the attenuation coefficient range (−200, −30) HU. The determination of MFT and EFT was done based on image adjustments with contrast improvements, texture features extraction utilizing the Gabor filter bank based on GLCM from image pixels, and pattern recognition classification algorithms. Finally, after the determination of cardiac fats, the volume of mediastinal and epicardial fat per milliliter was calculated using Eq. (1), and the correlation between cardiac fat volume and CAD was investigated using the FP-Growth algorithm and the SPSS software.

Volume of Cardiac fat = (Total Number of Fat Pixels*Slice Thickness*(Inch)^2)/(Dpi)^2 (1)

Given Eq. (1) and information of CT DICOM images is considered dpi=72 dots per inch, slice thickness =2 mm or 0.75 mm, and 1-inch =2.54cm. (See reference [13] for more details on the designed algorithm.)

Statistical Analysis

The patients' information in the first data set was analyzed using MATLAB R2018a to design an algorithm for the evaluation of the accuracy of the cardiac fat measurement. The patients' data collected from Madani Hospital were analyzed using the Statistical Package for the Social Sciences (SPSS, version 26.0) for Windows. Initial

information was described as a percentage or the mean ± the standard deviation (SD). The Spearman rho, the Kendall tau coefficient, and the Pearson linear correlation coefficient were used to calculate the association between various variables (eg, the correlation between CAD and cardiac fat volume.) The significance level in this study was considered to be 0.01.

RESULTS

The present study enrolled 120 patients to examine the correlation between CAD and cardiac fat volume. The patients' initial information was utilized to design an algorithm for the measurement of cardiac fat volume (Table 1).

Visually, the results of the cardiac fat determination of 2 slices were obtained from 2 different patients to design the algorithm shown in Figure 3. In this figure, the images of each column contain information regarding a patient, including a raw DICOM image and performed segmentation using the red, green, and blue colors such that the epicardial fat is red, mediastinal fat is green, and the pericardium layer between the 2 fats is blue. Gabor filters and texture features were used to design the algorithm of the cardiac fat determination, with an accuracy of 99.2%.

By doing the calculations of mediastinal and epicardial fat volumes for all 120 patients, the mean volume of epicardial fat in individuals with CAD was 111.35 ± 34.71 mL, the mean volume of epicardial fat in healthy individuals was 88.3 ± 3 1.73 mL, the mean volume of mediastinal fat in individuals with CAD was 69.73 ± 20.3 mL, the mean volume of mediastinal fat in healthy individuals was 53.27 ± 21.66 mL, the mean volume of thoracic fat (total cardiac fats) in individuals with CAD was 181.1 ± 52.29 mL, and the mean volume of thoracic fat in healthy individuals was 141.57 ± 5 0.78 mL. Given the considerable difference between variations in the stenosis of the coronary arteries in mediastinal fat volume and epicardial fat volume, we examined the correlation between the volume of cardiac fat tissue and CAD. There was a significant linear correlation between the volume of mediastinal, epicardial, and thoracic fats and CAD (Table 2). The correlations between the age of the patients, CAD, MFV, EFV, and thoracic fat volume (TFV) were assessed, and the results revealed positive correlations between age and EFV (r=0.255; P <0.01), MFV (r =0.383; P <0.001), and TFV (r =0.314; P <0.001). In this evaluation, the highest correlation was found between cardiac fat volume and CAD with thresholds of 140 mL for epicardial fat, 94 mL for mediastinal fat, and 220 mL for thoracic fat. There was, likewise, a positive correlation between the age of patients and CAD (r = 0.368; P <0.001). The results of a one-way ANOVA model for the statistical association analysis of cardiac fat tissue, age, and CAC in the stenosis of CAD and the low or high volume of cardiac fats (obtained by the threshold) are shown in Table 3. The variance analysis of cardiac fat volume in different degrees of stenosis of the coronary arteries showed a statistically significant difference between severe, moderate, and mild coronary artery occlusions and healthy individuals. The Scheffe post hoc test was used to follow the differences between the groups. The results of this test showed that the mean volume of epicardial (P <0.05), mediastinal (P =0.01), and thoracic (P <0.05) fats was significantly different between healthy individuals and those with severe coronary artery occlusion such that in healthy individuals, the mean volume of epicardial, mediastinal, and thoracic fats was significantly reduced by 30.88, 23.52, and 54.39 units, respectively, compared with the severe coronary artery occlusion group. The mean difference between the other groups was not

statistically significant. Table 4 also shows the results of 5 models of univariate and multivariate regression for predicting coronary artery obstruction through factors of cardiac fat volume, age, and sex. In this analysis, the stepwise method was employed for the multivariate regression model, in which the parameters of the best prediction model (obtained using mediastinal fat volume, age, and sex) are shown.

Table 1. Description of the patients' information

Characteristics	Data			
No. of patients	120			
Sex				
No. of women [a]	52 (43.33 %)	Health: 37 (71%)		
		CAD: 15 (28 %)		
No. of men [a]	68 (56.67 %)	Health: 40 (58 %)		
		CAD: 28 (41 %)		
Age (y) [b]	55.48 ± 12.6			
Coronary artery calcium scoring [c]	0.5 [0 – 1905]			
	severity of CAC			
	Healthy	Mild	Moderate	Severe
Epicardial fat volume (mL) [b]	88.3 ± 31.7	109.5 ± 35.9	105.6 ± 37.7	120.8 ± 29.9
Mediastinal fat volume (mL) [b]	53.3 ± 21.7	68.02 ± 19.6	65.2 ± 22.8	77.5 ± 17.4
Thoracic [d] fat volume (mL) [b]	141.6 ± 50.8	177.5 ± 51.7	170.8 ± 58.5	198.2 ± 44.9
Computed tomography imaging protocol	Siemens Medical solution, Forchheim, Germany 64 Slice scanner. (with considering Tube Voltage=120 kV, Current=175 mAs in Imaging, detector collimation of 1.2 mm, and gantry rotation time of 0.33 ms)			
Patient scan range	From the apex of the heart to the Tracheal Bifurcation section which has a resolution of 512 × 512, a pixel size of 0.68 × 0.68 mm^2, a thickness of 2 mm or 0.75 mm, and an average of 120 slices per patient.			

a .Information is provided as the number of patients (percentages).
b .Information is provided as the mean ± the standard deviation (SD).
c .Information is provided as the median and the range.
d. Thoracic adipose tissue = epicardial adipose tissue + mediastinal adipose tissue
CAD, Coronary artery disease

Table 2. Association between quantitative variables using the Spearman, Kendall, and Pearson correlation coefficients

Associations Between:	**Pearson** Linear Correlation Coefficient	**Kendall** Tau Coefficient	**Spearman** Rho
EFV [1] and CAD [2]	***r* = 0.322**; ***P* < 0.001**	*r* = 0.278; *P* < 0.01	*r* = 0.313; *P* = 0.001
EFV and MFV [3]	*r* = 0.819; *p* < 0.001	*r* = 0.63; *P* < 0.001	***r* = 0.822**; ***P* < 0.001**
EFV and TFV [4]	***r* = 0.971**; ***p* < 0.001**	*r* = 0.853; *P* < 0.001	*r* = 0.971;*P* < 0.001
MFV and CAD	*r* = 0.352; *p* < 0.001	*r* = 0.288; *P* < 0.001	***r* = 0.36**; ***P* < 0.001**
MFV and TFV	***r* = 0.932**; ***p* < 0.001**	*r* = 0.777; *P* < 0.001	*r* = 0.93; *P* < 0.001
TFV and CAD	***r* = 0.349**; ***p* < 0.001**	*r* = 0.277; *P* < 0.001	*r* = 0.345; *P* < 0.001

EFV, Epicardial fat volume; CAD, Coronary artery disease; MFV, Mediastinal fat volume; TFV, Thoracic fat volume
* Correlation in these calculations is significant at the 0.01 level (2-tailed).

Table 3. One-way analysis of variance for comparison between cardiac fat volume, coronary artery disease, age, and coronary artery calcium scoring

Analysis Between:		One-Way **ANOVA** Model
Independent Variables	Dependent Variables	
Stenosis of CAD [1]	Epicardial fat volume	F(3,116) = 4.776; *P* < 0.01
	Mediastinal fat volume	F(3,116) = 6.096; *P* = 0.001
	Thoracic fat volume	F(3,116) = 5.840; *P* = 0.001
	Age	F(3,116) = 6.109; *P* = 0.001
Epicardial fat volume [2]	Mediastinal fat volume	F(1,118) = 23.870; *P* < 0.001
	Thoracic fat volume	F(1,118) = 51.045; *P* < 0.001
	Age	F(1,118) = 2.440; *P* > 0.05
	CAC [5]	F(1,118) = 0.620; *P* > 0.05
Mediastinal fat volume [3]	Epicardial fat volume	F(1,118) = 26.635; *P* < 0.001
	Thoracic fat volume	F(1,118) = 40.186; *P* < 0.001
	Age	F(1,118) = 3.652; *P* > 0.05
	CAC	F(1,118) = 4.974; *P* < 0.05
Thoracic fat volume [4]	Epicardial fat volume	F(1,118) = 78.198; *P* < 0.001
	Mediastinal fat volume	F(1,118) = 65.413; *P* < 0.001
	Age	F(1,118) = 4.469; *P* < 0.05
	CAC	F(1,118) = 2.631; *P* > 0.05

Stenosis of healthy, mild, moderate, and severe for CAD
Two groups of the low and high volume of epicardial fat obtained with a threshold of 140 mL
Two groups of the low and high volume of mediastinal fat obtained with a threshold of 94 mL
Two groups of the low and high volume of thoracic fat obtained with a threshold of 220 mL
Coronary artery calcium (CAC) scoring
* The mean difference is significant at the 0.05 level.

Table 4. Results of univariate and multivariate regression analyses to predict coronary artery disease through cardiac fat volume, age, and gender

Type of Analysis	**Linear Regression** Models			Predictive Model Variables							
	Dependent Variables	Independent Variables	Equation Parameters	B [5]	Std. Error [5]	Beta [6]	t	*P*-value	R	Adjusted R Square	Std. Error of the Estimate
Univariate Analysis	Stenosis of CAD [1]	EFV [2]	(Constant)	-0.220	0.264	---	-0.833	*P* > 0.05	0.312	0.090	0.969
			EFV	0.009	0.003	0.312	3.568	*P* = 0.001			
		MFV [3]	(Constant)	-0.265	0.246	---	-1.078	*P* > 0.05	0.350	0.115	0.955
			MFV	0.016	0.004	0.350	4.053	*P* < 0.001			
		TFV [4]	(Constant)	-0.325	0.266	---	-1.223	*P* > 0.05	0.342	0.109	0.958
			TFV	0.006	0.002	0.342	3.954	*P* < 0.001			
		Age	(Constant)	-0.842	0.397	---	-2.121	*P* < 0.05	0.338	0.106	0.960
			Age	0.027	0.007	0.338	3.896	*P* < 0.001			
Multivariate analysis		EFV, MFV, TFV, Age, and Gender	(Constant)	-1.955	0.492	---	-3.971	*P* < 0.001	0.473	0.204	0.906
			MFV	0.013	0.004	0.297	3.359	*P* = 0.001			
			Age	0.020	0.007	0.247	2.821	*P* < 0.01			
			Gender	0.462	0.169	0.226	2.731	*P* < 0.01			

Stenosis of healthy, mild, moderate, and severe for coronary artery disease
EFV, Epicardial fat volume; MFV, Mediastinal fat volume; TFV, Thoracic fat volume
Unstandardized Coefficients
Standardized Coefficient

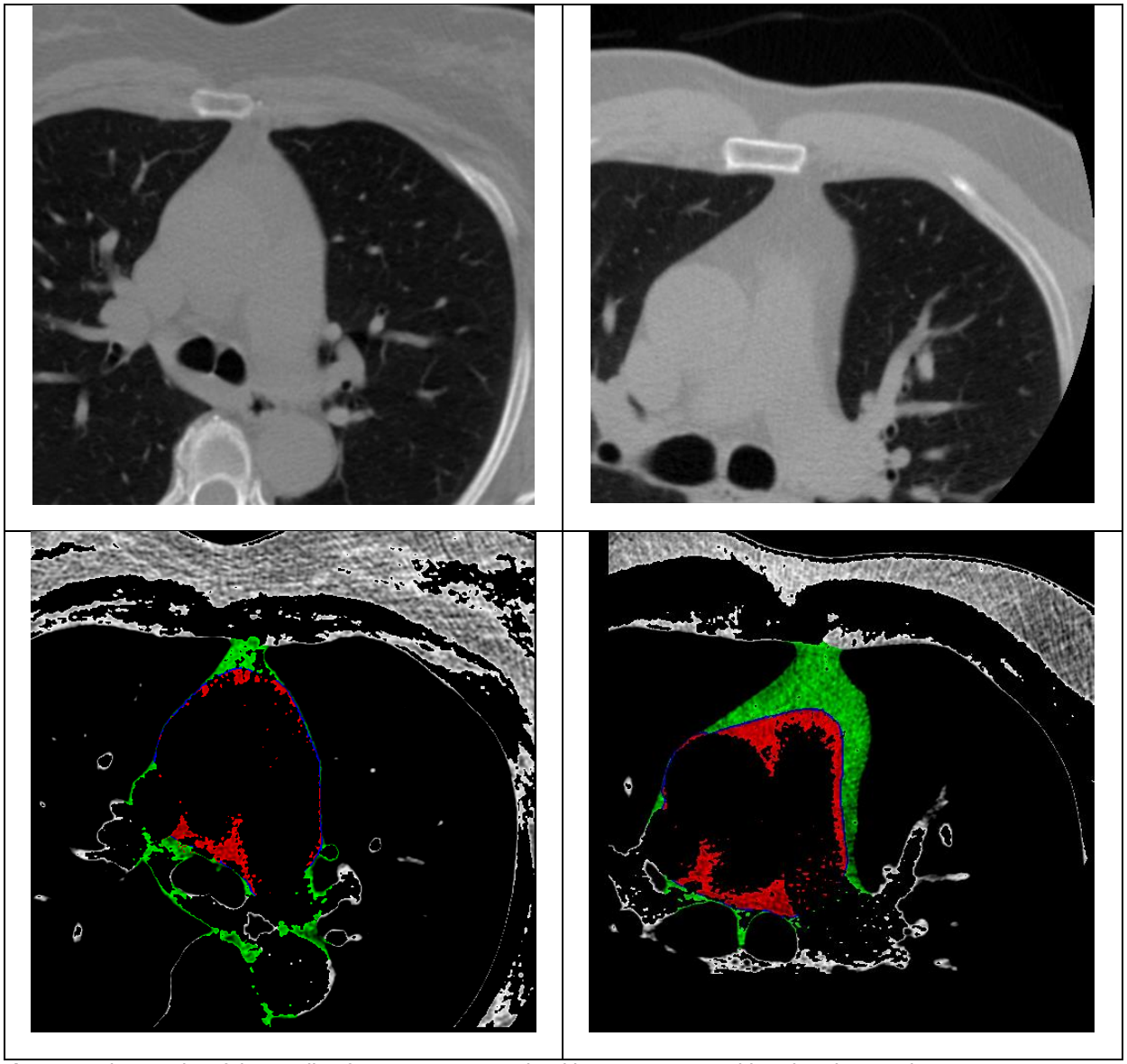

Figure 3. The results of the cardiac fat measurement algorithm are presented herein. First row images: raw DICOM images, second-row images: determination of fats using the designed algorithm

DISCUSSION

In this study, we developed an instrument for the automated measurement of cardiac fat in non-contrast CT images, and we determined coronary artery stenosis using a coronary calcium scoring assessment. Our results showed that the accurate measurement of cardiac fat from non-contrast CT images was feasible and reproducible and that the volume of cardiac fat had a positive correlation with age, CAD, and each other. This technique allows for the reliable extraction of patients' cardiovascular risk information from a cardiac CT scan. Our results also demonstrated that the volume of mediastinal, epicardial, and thoracic fats was lower in subjects without CAD than in those with CAD. Alterations within MFT and EFT volumes could also be related to various factors of CAD, including adverse cardiovascular events, [14, 15] heart

arrhythmias, [16] myocardial ischemia, [17, 18] coronary artery stenosis, [19] increased prevalence of coronary artery calcification, [20] myocardial infarction, high diastolic fillings, incompatible plaque characteristics, [21–23] metabolic syndromes, [24] pathophysiologies of atrial fibrillation, [25] extracranial carotid artery atherosclerosis, baseline sympathetic nerve activity, [26] and conventional metabolic risk factors such as hypertension, [27] impaired fasting glucose, hyperlipidemia, high body mass index, and especially, type II diabetes mellitus. [28] In conclusion, it can be stated that the determination of cardiac mediastinal and epicardial fats in non-contrast CT images may predict potential ischemia and improve cardiovascular risk assessment. Therefore, the measurement of cardiac adipose tissue without extra radiation or contrast in CT images may provide an evaluation of plaque and coronary artery stenosis, which can prepare data on the extra risk factor for cardiovascular occasions. In this study, different thresholds for the volume of mediastinal, epicardial, and thoracic fats were investigated using the FP-Growth algorithm to determine the highest correlation and association with CAD. Based on the obtained threshold values for cardiac fat, it can be stated that patients who have a fat volume of less than the threshold value may not be susceptible to CAD and patients who have a fat volume exceeding the threshold value may be susceptible to CAD. Such information may prevent unnecessary invasive angiography. Moreover, the design of our multivariate regression model showed that according to the parameter “adjusted R square”, 3 subscales of mediastinal fat, age, and sex predicted 20.4% of the variance of coronary artery stenosis. Given the *P*-value of each variable, these 3 subscales significantly predicted coronary artery stenosis. According to the beta criterion, it can be stated that by increasing 1 SD in the amount of mediastinal fat, the coronary artery occlusion rate will increase by 0.297 SD. Additionally, by increasing 1 SD in age, the rate of coronary artery occlusion will increase by 0.247 SD. These interpretations were also obtained from the results of our univariate regression model. The markers of inflammation and other risk factors of CAD such as diabetes mellitus, smoking, and body mass index were not considered in our work, and these risk factors and markers may provide extra assistance for a causal association between CAD and cardiac fat tissues.

CONCLUSIONS

The results of the current study showed that a low volume of thoracic, mediastinal, and epicardial fats was correlated with healthy subjects, whereas a high volume of thoracic, mediastinal, and epicardial fats was correlated with subjects with CAD. Consequently, the evaluation of cardiac fat could be utilized as a trustworthy imaging biomarker to aid the specialist in the computer-aided diagnosis of metabolic risks and cardiovascular diseases, especially CAD, and the progress of their outcomes with a view to avoiding unessential invasive angiography. This work will be necessary because of the sheer volume of data in need of analysis, significant differences between observers, insufficient accuracy on the part of medical technicians, and costs. However, a new field of research is required for future development and analysis to examine the correlation between cardiac adipose tissue and cardiovascular diseases by designing a reliable biomarker tool aimed at predicting cardiovascular diseases.

Acknowledgments

This study was financially supported by the Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences (No. 5/88/1782). This article was written based on an MS dissertation, registered in Tabriz University of Medical Sciences.

Conflict of Interest and Financial Disclosure

The protocol of this study was confirmed by the Ethics Committee of Tabriz University of Medical Sciences (approval ID: IR.TBZMED.REC.1398.122). The authors declare that they have no potential or actual conflicts of interest.

REFERENCES

1. Aslanabadi N, Salehi R, Javadrashid A, Tarzamani M, Khodadad B, Enamzadeh E, et al. Epicardial and Pericardial Fat Volume Correlate with the Severity of Coronary Artery Stenosis. *Journal of Cardiovascular and Thoracic Research* 2014;6:235–239.

2. Iacobellis G, Pistilli D, Gucciardo M, Leonetti F, Miraldi F, Brancaccio G, et al. Adiponectin expression in human epicardial adipose tissue in vivo is lower in patients with coronary artery disease. *Cytokine* 2005;29:251–255.

3. Kortelainen M-L. Myocardial infarction and coronary pathology in severely obese people examined at autopsy. *International Journal of Obesity* 2002;26:73–79.

4. Sarin S, Wenger C, Marwaha A, Qureshi A, Go BDM, Woomert CA, et al. Clinical Significance of Epicardial Fat Measured Using Cardiac Multislice Computed Tomography. *The American Journal of Cardiology* 2008;102:767–771.

5. Sacks HS, Fain JN. Human epicardial adipose tissue: A review. *American Heart Journal* 2007;153:907–917.

6. Ct N, Dey D, Suzuki Y, Suzuki S, Ohba M. Automated Quantitation of Pericardiac Fat From. *Ratio* 2008;43:145–153.

7. Sicari R, Sironi AM, Petz R, Frassi F, Chubuchny V, De Marchi D, et al. Pericardial rather than epicardial fat is a cardiometabolic risk marker: An MRI vs echo study. *Journal of the American Society of Echocardiography* 2011;24:1156–1162.

8. Talman AH, Psaltis PJ, Cameron JD, Meredith IT, Seneviratne SK, Wong DTL. Epicardial adipose tissue: far more than a fat depot. *Cardiovascular diagnosis and therapy* 2014;4:416–41629.

9. Coppini G. Quantification of Epicardial Fat by Cardiac CT Imaging. *The Open Medical Informatics Journal* 2011;4:126–135.

10. Polonsky TS, McClelland RL, Jorgensen NW, Bild DE, Burke GL, Guerci AD, et al. Coronary Artery Calcium Score and Risk Classification for Coronary Heart Disease Prediction. *JAMA* 2010;303:1610.

11. Rodrigues O, Morais FFC, Morais NAOS, Conci LS, Neto L V., Conci A. A novel approach for the automated segmentation and volume quantification of cardiac fats on computed tomography. *Computer Methods and Programs in Biomedicine* 2016;123:109–128.

12. Miller NE, Thelle DS, Førde OH, Mjøs OD, Ouweneel AB, Van Eck M, et al. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, Single Volume, 11th Edition. *New England Journal of Medicine* 2019.

13. Kazemi A, Keshtkar A, Rashidi S, Aslanabadi N, Khodadad B, Esmaeili M. Segmentation of cardiac fats based on Gabor filters and relationship of adipose volume with coronary artery disease using FP-Growth algorithm in CT scans. *Biomedical Physics & Engineering Express* 2020.

14. Cheng VY, Dey D, Tamarappoo B, Nakazato R, Gransar H, Miranda-Peats R, et al. Pericardial fat burden on ECG-Gated noncontrast CT in asymptomatic patients who subsequently experience adverse cardiovascular events. *JACC: Cardiovascular Imaging* 2010;3:352–360.

15. Mahabadi AA, Berg MH, Lehmann N, Kälsch H, Bauer M, Kara K, et al. Association of Epicardial Fat With Cardiovascular Risk Factors and Incident Myocardial Infarction in the General Population. *Journal of the American College of Cardiology* 2013;61:1388–1395.

16. Scherschel K, Gosau N. EAT: What role does the fat around the heart play? *International Journal of Cardiology* 2020;301:121–122.

17. Janik M, Hartlage G, Alexopoulos N, Mirzoyev Z, McLean DS, Arepalli CD, et al. Epicardial adipose tissue volume and coronary artery calcium to predict myocardial ischemia on positron emission tomography-computed tomography studies. *Journal of Nuclear Cardiology* 2010;17:841–847.

18. Tamarappoo B, Dey D, Shmilovich H, Nakazato R, Gransar H, Cheng VY, et al. Increased Pericardial Fat Volume Measured From Noncontrast CT Predicts Myocardial Ischemia by SPECT. *JACC: Cardiovascular Imaging* 2010;3:1104–1112.

19. Hirata Y, Tabata M, Kurobe H, Motoki T, Akaike M, Nishio C, et al. Coronary Atherosclerosis Is Associated With Macrophage Polarization in Epicardial Adipose Tissue. *Journal of the American College of Cardiology* 2011;58:248–255.

20. Gorter PM, de Vos AM, van der Graaf Y, Stella PR, Doevendans PA, Meijs MFL, et al. Relation of Epicardial and Pericoronary Fat to Coronary Atherosclerosis and Coronary Artery Calcium in Patients Undergoing Coronary Angiography. *The American Journal of Cardiology* 2008;102:380–385.

21. Alexopoulos N, McLean DS, Janik M, Arepalli CD, Stillman AE, Raggi P. Epicardial adipose tissue and coronary artery plaque characteristics. *Atherosclerosis* 2010;210:150–154.

22. Konishi M, Sugiyama S, Sugamura K, Nozaki T, Ohba K, Matsubara J, et al. Association of pericardial fat accumulation rather than abdominal obesity with coronary atherosclerotic plaque formation in patients with suspected coronary artery disease. *Atherosclerosis* 2010;209:573–578.

23. Rajani R, Shmilovich H, Nakazato R, Nakanishi R, Otaki Y, Cheng VY, et al. Relationship of epicardial fat volume to coronary plaque, severe coronary stenosis, and high-risk coronary plaque features assessed by coronary CT angiography. *Journal of Cardiovascular Computed Tomography* 2013;7:125–132.

24. Dey D, Wong ND, Tamarappoo B, Nakazato R, Gransar H, Cheng VY, et al. Computer-aided non-contrast CT-based quantification of pericardial and thoracic fat and their associations with coronary calcium and metabolic syndrome. *Atherosclerosis* 2010;209:136–141.

25. Zhao L, Gould PA, Ng ACT, Wang WYS. Cardiac autonomic nerve system and epicardial fat in atrial fibrillation. *International Journal of Cardiology* 2020;303:58–59.

26. Kawasaki M, Yamada T, Furukawa Y, Morita T, Tamaki S, Kida H, et al. Are cardiac sympathetic nerve activity and epicardial adipose tissue associated with atrial fibrillation recurrence after catheter ablation in patients without heart failure? *International Journal of Cardiology* 2020;303:41–48.

27. Kropidlowski C, Meier-Schroers M, Kuetting D, Sprinkart A, Schild H, Thomas D, et al. CMR based measurement of aortic stiffness, epicardial fat, left ventricular myocardial strain and fibrosis in hypertensive patients. *IJC Heart and Vasculature* 2020;27:100477.

28. Reinhardt M, Cushman TR, Thearle MS, Krakoff J. Epicardial adipose tissue is a predictor of decreased kidney function and coronary artery calcification in youth- and early adult onset type 2 diabetes mellitus. *Journal of Endocrinological Investigation* 2019;42:979–986.