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RADIOMIC FEATURES OF EPICARDIAL ADIPOSE TISSUE IN CORONARY ATHEROSCLEROSIS

E.V. Popov, Zh.Zh. Anashbaev, A.N. Maltseva, S.I. Sazonova

Cardiology Research Institute, Federal State Budgetary Scientific Institution "Tomsk National Research Medical Center of the Russian Academy of Sciences", 111a, St. Kievskaya, Tomsk, Russian Federation, 634012

Highlights

• Radiomics is considered to be a promising method for getting some quantitative data from the diagnostic images. The information about epicardial adipose tissue changes in atherosclerotic lesions of the coronary arteries can be used as an early diagnostic criterion of coronary heart disease. No similar research in radiomics was conducted before.

Aim To investigate the association of the radiomic characteristics of epicardial adipose tissue (EAT) on contrast-free computed tomography (CT) of the heart with the severity of obstructive coronary lesion and myocardial ischemia.

Methods The study included 68 patients with coronary heart disease (mean age of 63.5±9.4, 45 men and 23 women), and 15 patients (mean age 30±4.8; 14 men and 1 woman) without cardiovascular disease as a control group. All the patients underwent multispiral computed coronary angiography, coronary calcium scores (CCS) determination and stress myocardial perfusion scintigraphy. Radiomic characteristics of EAT (texture analysis by gradations of gray color) were determined on non-contrast computer tomogram images of the heart using 3D-Sliser software and the SliserRadiomics module (version 4.10.2). The obtained indicators were compared between a control and under the study groups as well as between subgroups of patients divided according to the degree of obstruction of the coronary arteries, the size of the perfusion defect, and the value of the CCS.

Results The comparative analysis of radiomic indicators of EAT between patients with coronary artery disease and the control group showed the presence of statistically significant differences between them. At the same time, the correlation analysis in the study group did not reveal any correlations between the radiomic parameters and the size of the perfusion defect, CCS or degree of stenosis of the lumen of the coronary arteries.

Conclusion The textural characteristics of EAT in patients with coronary heart disease differ from those in individuals without cardiovascular pathology. At the same time, these indicators are not associated with the severity of obstructive lesions of the coronary arteries, the value of the CCS, and the size of the perfusion defect according to scintigraphy.

Keywords Coronary atherosclerosis • Cardiac ischemia • Radiomics • Texture analysis

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Список сокращений

CHD	– coronary heart disease	CACS	– coronary artery calcium scoring
EAT	– epicardial adipose tissue	CCS	– coronary artery score
CA	– coronary arteries	CT	– computed tomography

Introduction

Despite the active measures taken in recent decades to prevent and treat cardiovascular diseases, coronary heart disease (CHD) remains one of the leading causes of mortality among the working population worldwide [1, 2]. The determination of cardiovascular risk is decisive for the choice of coronary heart disease treatment method and of a preventive medicine for adverse cardiovascular events. In this regard, it is relevant to search for the markers that allow the most

Corresponding author: *Evgeniy V. Popov, popov-yevgeniy92@mail.ru; address: 111a, St. Kievskaya, Tomsk, Russia, 634012*

accurate prediction of the coronary arteries (CA) atherosclerotic lesions in a patient.

In recent years the possibility of using the epicardial adipose tissue (EAT) volume indicator determined by various imaging methods (echocardiography, computed tomography (CT)) as one of such markers has been actively investigated. Numerous studies [3, 4] showed that epicardial adipose tissue (EAT) is a complex endocrine organ producing a number of biologically active substances – adipokines, capable of diffusing into the intima-media layer of a nearby vessel, affecting its vasomotor function and leading to an inflammatory response [5, 6]. The close anatomical proximity of the EAT to the CA may cause local inflammation which contributes to the formation and growth of soft-tissue (uncalcified) atherosclerotic plaques and subsequent adverse clinical events.

CT, with its high tissue resolution and reproducibility, is currently the leading method of diagnosing many diseases including cardiologic ones. Consequently the use of CT to measure the volume parameters of the EAT seems to be the most accurate and justified. In recent years several large-scale studies have been conducted [5–7] in which an attempt was made to identify the association of the EAT volume index with the presence and severity of atherosclerotic CA lesion but the authors received negative results. We supposed that the growth of atherosclerotic plaques in the heart vessels may be more influenced not by qualitative but by quantitative characteristics of the EAT reflecting its structure and distribution in the heart. To get such characteristics on CT images an ultra-modern developing medical technology related to personalized medicine, radiomics can be used [8]. Radiomics is a method of computer processing of medical images that converts them into numerical data calculated in large quantities using software applications. The numerical data obtained are unique for each patient. They determine many structural characteristics of the tissue under study which cannot be visually detected. In the Modern literature does not have any works in which the relationship between the radiometric characteristics of EAT on contrast-free CT images and the severity of obstructive CA damage and myocardial ischemia has been studied.

The aim of the study – to investigate the association of the radiomic characteristics of EAT on contrast-free heart CT scans with the severity of obstructive coronary lesion and myocardial ischemia.

Methods

The study included 68 patients (mean age of 63.5±9.4 years; 45 men and 23 women) with coronary heart disease functional class I–III. They underwent examination and treatment at the Research Institute of Cardiology of Tomsk Scientific Research Medical Centre in 2013–2019. (Tomsk, Russia). The group under the study consisted of 15 individuals (of mean age 30±4.8 years; 14 men and 1 woman) without cardiovascular diseases. The study was approved at the meeting of the Institution Committee on Biomedical ethics (Protocol No. 134 of June 11, 2015). The clinical characteristics of the study group participants are presented in Table 1.

The criteria for inclusion of patients under the study: 1) age ≥18 and <80 years; 2) chronic coronary syndrome; 3) sinus rhythm.

The criteria for exclusion: 1) acute coronary syndrome or stroke less than a month ago; 2) myocardial revascularization in anamnesis; 3) acute coronary syndrome or revascularization between single-photon emission computed tomography and coronary angiography; 4) unstable hemodynamics; 5) heart failure >III Functional Class according to NYHA; left ventricular ejection fraction <40%; 6) valvular heart lesions with a degree of stenosis or insufficiency >I; 7) inflammatory heart diseases; 8) cardiomyopathy; 9) atrial fibrillation; 10) atrioventricular block >I art.; 11) severe forms of pulmonary pathology leading to respiratory failure (bronchial asthma, severe forms of chronic obstructive pulmonary disease); 12) body mass index >40 kg/m^2; 13) non-cardiac diseases in the decompensation phase; 14) allergy to iodine, hypersensitivity to pharmacological stress agents (adenosine triphosphate); 15) renal insufficiency >II art.; 16) non-compliance with at least one of the inclusion criteria.

During hospitalization, all patients had a complete clinical and instrumental examination, which included perfusion scintigraphy of the myocardium with 99mTs-methoxy-isobutyl-isonitrile (Technetril, 99mTs, Public Corporation "Diamed", Russia) and multispiral computer coronaroangiography [9].

Perfusion scintigraphy of the myocardium was performed according to the two–day "load-rest" protocol

Table 1. Clinical characteristics of patients in the study group

Parameter	Value
Age, M±m	63,5±9,4
CAD propability %, M±m	44±25
NYHA Classification – The Stages of Heart Failure	I–III
Hypertonic disease, %	85
Diabetes, %	12
Smoking, %	19
Obesity, %	51
Hypercholesterolemia, %	45

Note: *CAD – coronary heart disease; NYHA – New York Heart Association.*

with attenuation correction (low-dose computed tomography), in accordance with the recommendations of the European Society of Nuclear Medicine [10].

To determine the calcium score contrast-free CT of the heart region was performed with prospective ECG synchronization and further reconstruction in the 75% phase of the R-R interval of the cardiac cycle. The coronary calcium scoring was calculated semi-automatically on the Advantage Workstation 4.3 (GE Healthcare).

The stress test was performed using intravenous infusion of adenosine triphosphate at a dose of 140 mcg/kg/min. Image recording – 90 minutes after the introduction of the radiopharmaceutical on a hybrid single-photon emission and X-ray computed tomograph GE Discovery NM/CT 570c (GE Healthcare; Milwaukee, Wisconsin, USA) using a low-energy multi-Pinhole collimator (Multi-Pinhole collimator) in 19 projections into a 32 × 32 pixel matrix (pixel size 4 mm).

The images were reconstructed on a specialized workstation (Xeleris II, GE Healthcare; Haifa, Israel). The data obtained were processed using the software Corridor4DM (4DM, Invia Medical Imaging Solutions; Ann Arbor, Michigan, USA) with the reorientation of the left ventricle along the short and long axes of the heart, as well as the construction of a 17-segmental polar map of the left ventricle. The local myocardial perfusion disorders analysis in each segment was carried out visually and quantitatively on a 5-point scale (from 0 to 4) with the calculation of the total index of perfusion disorders under the stress (SSS) and at rest (SRS) calculated as the sum of points in hypoperfused segments [11–13].

To measure the calcium score contrast-free CT of the heart region was performed with prospective ECG synchronization and further reconstruction in the 75% phase of the R-R interval of the cardiac cycle. The coronary calcium score (CCS) was calculated semi-automatically on the Advantage Workstation 4.3 (GE Healthcare).

The heart multispiral computed tomography was made from the level of tracheal bifurcation to the diaphragm with respiratory delay (6–8 s). Intravenous infusion of yopamidol (370 mg of iodine/ml) ("Yopamiro", Bracco, Italy) in volume of 60-110 ml at a rate of 4–5.5 ml/s was used to contrast the CA. The study was recorded in a retrospective ECG synchronization mode. The recorded parameters were as follows: 120 kV tube voltage, 300–600 mA current with ECG modulation, 0.4 s tube rotation speed, 0.20–0.22 pitch (depending on heart rate). The images were reconstructed according to standard protocols with a slice thickness of 0.625 mm. The computed tomography series was processed on the Advantage Workstation 4.3 (GE Healthcare) workstation.

The radiomic characteristics were obtained using the 3D-Slicer software and the Radiomics module (version 4.10.2). Segmentation of the EAT on a contrast-free CT was performed by a semi-automatic method. The area of interest was isolated from the bifurcation of the pulmonary trunk to the base of the heart, taking into account the density of adipose tissue (from -190 to -30 HU) (Fig. 1). Using the SliserRadiomics extension radiomic indicators were obtained: first-order statistics; second-order statistics (gray level coincidence matrix – GLCM, gray level dependency matrix – GLDM, gray level mileage matrix – GLRM, gray level zone matrix – GLZM, matrix of differences of neighboring gray levels – NGLDM) [4]. The total number of received radiomic indicators was 93. Taking into account the experience of using radiomic indicators in the previous studies [14–18] the following indicators were selected for analysis characterizing the distribution of gray color in images and the uniformity of the EAT structure:

1. **high gray level emphasis (HGLE)** – characterizes the distribution of higher gray level values in images;
2. **gray level nonuniformity (GLN)** – characterizes the similarity of the gray level intensity values in the image;
3. **autocorrelation** – is a measure of the magnitude of the fineness and roughness of the texture;
4. **skewness** – measures the asymmetry of the values distribution relative to the average value;
5. **run percentag**e – characterizes the roughness of the tissue texture;

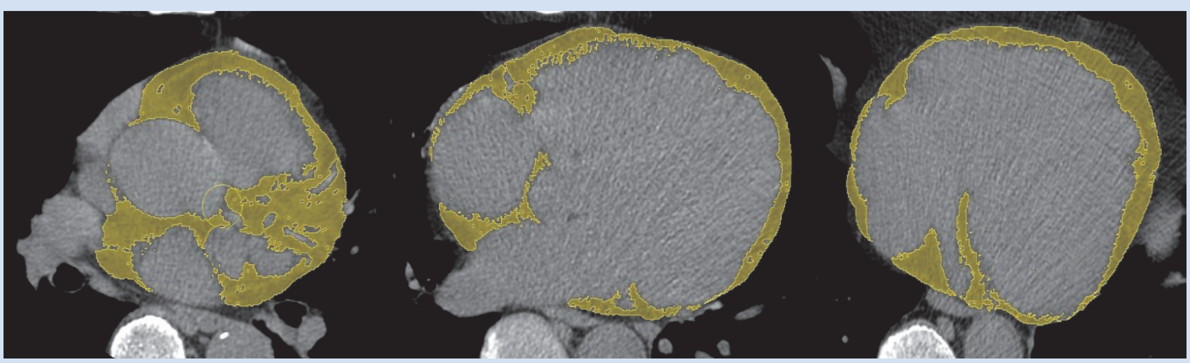

Figure 1. Segmentation of epicardial adipose tissue in non-contrast images of the heart. Highlighted epicardial adipose tissue is shown in yellow

6. **gray level variance (GLV)** – characterizes the dispersion of the gray intensity level;

7. **size zone nonuniformity (SZN)** – characterizes the variability of the dimensional zones volumes in the image;

8. **busyness** – a measure of the transition from a pixel to a neighboring pixel. A high value for busy indicates a "busy" image with rapid intensity changes between pixels and its neighbors [19].

Statistical Analysis

To determine the nature of the distribution of the obtained data, the Shapiro–Wilk normality criterion was used (the distribution was considered normal at p>0.05). To describe quantitative indicators, interquartile intervals (25th and 75th percentiles) were used for aggregates that do not obey the law of normal distribution. The statistical significance of the intergroup differences in values was assessed using the nonparametric Mann-Whitney test. The evaluation of correlations between pairs of quantitative features was carried out using a nonparametric Spearman rank coefficient.

The study design is shown in Fig. 2.

Results

A comparative analysis of the EAT radiomic parameters in patients with coronary heart disease and the control group showed statistically significant differences in all parameters (Table 2). At the same time according to the results of the correlation analysis in the study group, there was no relationship between radiomic parameters and the size of the perfusion defect against the background of a stress test, the value of CCS, the degree of CA stenosis (Table 3).

Further, we assumed that the EAT texture undergoes changes as the atherosclerotic lesion of the spacecraft progresses, which may be indicated by radiomic characteristics. We used three options for dividing the group of patients with coronary heart disease into subgroups in order to perform the analysis (Fig. 2).

Option 1. Depending on the degree of CA stenosis [10, 20]: 1st subgroup – less than 50% (n = 37); 2nd subgroup – with stenosis of 50% or more (n = 31). However, the comparison of the radiomic indicators between them did not show statistically significant differences (Table 4).

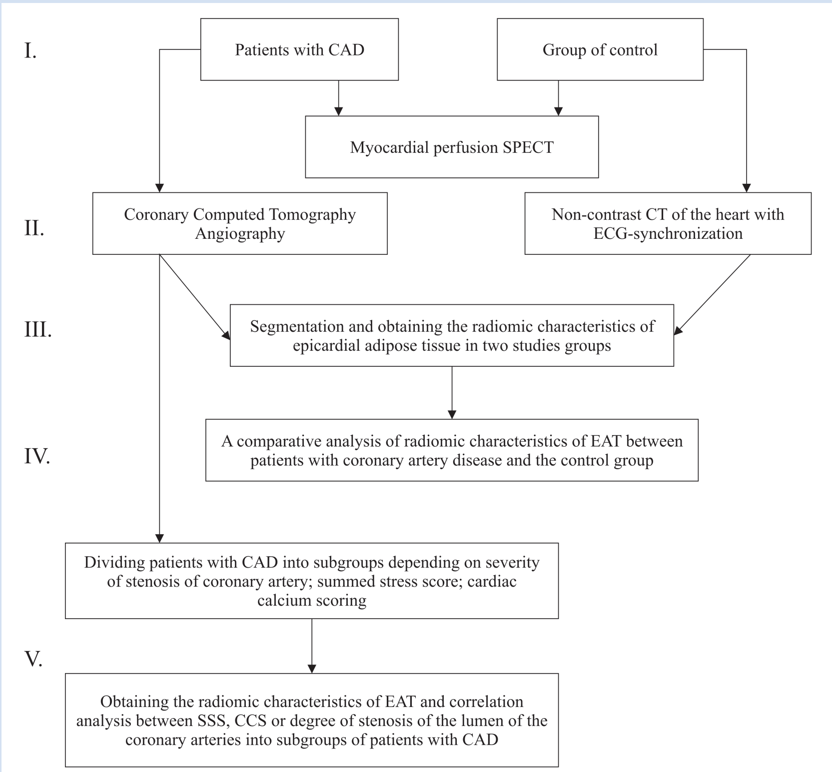

Figure 2. Study design
Note: *CAD – coronary heart disease; CCS – coronary calcium scoring; CT – computed tomography; EAT – epicardial adipose tissue; ECG – electrocardiography; SSS – summed stress score.*

Table 2. Comparative analysis of the radiomic characteristics of epicardial adipose tissue of patients with coronary artery disease and the control group

Radiomic features	Patients with CAD (n = 68), Me (Q 25; Q 75)	Control (n = 15), Me (Q 25; Q 75)	p
HGLE	28.05 (26.51; 29.32)	30.03 (29.45; 30.49)	0.000657
GLN	49 034.37 (40 394.35; 61 709)	36 584 (32 651.7; 42 074.7)	0.008509
Autocorrelation	25.29 (23.83; 26.26)	26.98 (26.06; 27.41)	0.013558
Skewness	-0.29 (-0.48; -0.18)	-0.68 (-0.72; -0.63)	0.000009
GLV	1.89 (1.78; 1.99)	2.36 (2.30; 2.48)	0.000007
Run Percentage	0.77 (0.74; 0.79)	0.81 (0.77; 0.85)	0.023005
SZN	4 295.87 (3 541.88; 5 363.95)	6 607.1 (6 234.47; 7 797.56)	0.000093
Byseness	1 002.4 (829.72; 1 371.96)	793.15 (688.85; 939.03)	0.024418

Note: *CHD – coronary heart disease; CAD – coronary artery disease GLN – gray level nonuniformuty; GLV – gray level variance; HGLE – high gray level emphasis; SZN – size zone nonuniformity.*

Option 2. Depending on CCS [21]: 1st subgroup, 1–100 – minimal and insignificant damage CA (n = 36); 2nd subgroup, more than 101 – moderate and severe damage to the CA (n = 32). The analysis also failed to identify statistically significant differences (Table 5).

Option 3. Depending on the size of the perfusion defect [11, 22], against the background of the stress test: the 1st subgroup with perfusion defects of less than 7 points (n = 48); the 2nd subgroup – with perfusion defects of more than 7 points (n = 20). Subsequent statistical analysis revealed no significant differences.

Discussion

This study demonstrates that the radiomic characteristics of EAT in patients with atherosclerotic CA lesions differ from those in patients without cardiovascular pathology. This may indicate early changes in the texture of the EAT which do not change as the disease progresses. It has already been shown that an increase in the volume of EAT is associated with the severity of coronary heart disease [3, 6, 7, 14, 23]. A number of studies have also revealed that the volume of EAT increases regionally in the area of uncalcified atherosclerotic plaques correlates with regional myocardial ischemia and increased perivascular expression of adipocytes [5, 24]. At the same time the volume of the EAT retains unchanged values in the area of the normal myocardium or the scar zone [7]. However, it has not yet been possible to fully

Table 3. Analysis of the correlation between the radiomic characteristics of epicardial adipose tissue and the size of the perfusion defect against the background of the stress test, the coronary calcium score and the degree of coronary artery stenosis in patients with coronary artery disease

Radiomic features	Spearman's correlation coefficient (*p*)		
	SSS	CCS	Severity of stenosis CA
HGLE	-0.28	-0.26	-0.29
GLN	0.2	0.21	0.23
Autocorrelation	-0.25	-0.23	-0.23
Skewness	0.3	0.34	-0.34
GLV	0.18	-0.25	-0.34
Run Percentage	-0.1	-0.2	-0.24
SZN	-0.3	-0.27	-0.26
Byseness	0.2	0.16	0.18

Note: *CA – coronary artery; CCS – coronary calcium scoring; GLN – gray level nonuniformuty; GLV – gray level variance; HGLE – high gray level emphasis; SSS – summed stress score; SZN – size zone nonuniformity.*

Table 4. Radiomic characteristics of epicardial adipose tissue on CT images of the heart of patients with coronary artery disease, in subgroups separated by the degree of stenosis of the coronary arteries

Radiomic features	Patients with stenosis up to 50% (n = 37), Me (Q 25; Q 75)	Patients with stenosis over 50% (n = 31), Me (Q 25; Q 75)	p
HGLE	28.09 (26.63; 29.32)	27.52 (26.21; 28.56)	0.191
GLN	51 558.25 (41 010.89; 61 708.57)	48 673.76 (41 162.9; 63 805.29)	0.902
Autocorrelation	25.48 (24.08; 26.31)	24.86 (23.63; 25.99)	0.179
Skewness	-0.30 (-0.48; -0.19)	-0.27 (-0.43; -0.1)	0.248
GLV	1.88 (1.78; 1.98)	1.85 (1.76; 1.94)	0.603
Run Percentage	0.76 (0.74; 0.79)	0.76 (0.73; 0.79)	0.358
SZN	4 308.23 (3 819.36; 5 031.41)	4 017.37 (3 253.09; 5 116.91)	0.346
Byseness	1 068.87 (829.72; 1 371.96)	1 002.86 (855.06; 1 302.69)	0.921

Note: *GLN – gray level nonuniformuty; GLV – gray level variance; HGLE – high gray level emphasis; SZN – size zone nonuniformity.*

Table 5. Radiomic characteristics of epicardial adipose tissue of patients with coronary artery disease in subgroups, divided by the value of the calcium score

Radiomic features	Patients with CCS = 1–100 (n = 36), Me (Q 25; Q 75)	Patients with CCS = 101 (n = 32), Me (Q 25; Q 75)	p
HGLE	28.06 (26.85; 29.4)	27.56 (26.28; 28.78)	0.237
GLN	48 673.76 (39 962.85; 56 378.03)	50 365.88 (41 271.56; 64 895.94)	0.349
Autocorrelation	25.30 (24.41; 26.36)	24.79 (23.7; 26.08)	0.2
Skewness	-0.29 (-0.49; -0.20)	-0.27 (-0.46; -0.1)	0.183
GLV	1.87 (1.78; 1.99)	1.88 (1.76; 1.95)	0.629
Run Percentage	0.77 (0.74; 0.79)	0.76 (0.73; 0.79)	0.452
SZN	4 392.46 (3 466.07; 5 197.68)	4 107.26 (3 421.84; 5 178.05)	0.505
Byseness	1 011.31 (811.20; 1 332.84)	1 042.14 (832.50; 1 566.55)	0.647

Note: *CCS – coronary calcium scoring; GLN – gray level nonuniformuty; GLV – gray level variance; HGLE – high gray level emphasis; SZN – size zone nonuniformity.*

Table 6. Radiomic characteristics of epicardial adipose tissue of patients with coronary artery disease, divided by summed stress score

Radiomic features	SSS <7 (n = 48), Me (Q 25; Q 75)	SSS >7 (n = 31), Me (Q 25; Q 75)	p
HGLE	28.05 (26.38; 28.94)	27.60 (26.51; 28.65)	0.23
GLN	49 637.04 (40 394.35; 61 961.71)	50 220.11 (42 148.77; 64 106.86)	0.9
Autocorrelation	25.51 (23.93; 26.1)	24.86 (23.66; 25.69)	0.163
Skewness	-0.29 (-0.47; -0.18)	-0.28 (-0.46; -0.19)	0.109
GLV	1.86 (1.77; 1.95)	1.89 (1.79; 2.08)	0.527
Run Percentage	0.75 (0.73; 0.79)	0.77 (0.75; 0.78)	0.315
SZN	4 276.57 (3 541.88; 4 747.02)	4 257.37 (3 286.95; 5 294.92)	0.315
Byseness	974.61 (829.72; 1 327.39)	1 020.22 (891.92; 1 509.57)	0.9

Note: *GLN – gray level nonuniformuty; GLV – gray level variance; HGLE – high gray level emphasis; SSS – summed stress score; SZN – size zone nonuniformity.*

determine the causal relationship between myocardial ischemia and the volume of EAT.

Our study shows that there is no association between the textural characteristics of the EAT and the severity of CA stenosis, the size of the perfusion defect and the coronary calcium score. This indicates that radiomic indicators of EAT on contrast-free CT images of the heart cannot be used as a marker for predicting atherosclerotic lesion of the patient. It is likely that this method of processing and analyzing CT images may have a higher prognostic value in contrast studies.

It has recently been demonstrated that the use of radiomic analysis increases the diagnostic accuracy of multispiral computed coronary angiography in identifying specific markers of vulnerability of atherosclerotic plaques which was confirmed by the data from intravascular ultrasound and optical coherence tomography [15–18, 25]. Another study revealed the relationship of radiomic CT characteristics of atherosclerotic plaques and perivascular adipose tissue with the results of positron emission tomography with NaF18, visualizing the inflammatory process [14–18].

Thus, radiomic image analysis in cardiology opens up prospects for identifying new markers of various pathological processes that can be used both to detect early tissue changes and to predict the disease. However, to understand the effectiveness of this approach, further studies on large samples and comparison of the data obtained by textural analysis with other research methods, such as various modalities of radiation diagnostics, laboratory studies, histological verification, are necessary.

Conclusion

Textural characteristics of epicardial adipose tissue of patients with ischemic heart disease differ from those of individuals without cardiovascular pathology. At the same time, these indicators are not associated with the severity of obstructive coronary artery disease, the value of the coronary calcium score, as well as the size of the perfusion defect according to scintigraphy.

Conflict of Interest

E.V. Popov declares no conflict of interest. Zh.Zh. Anashbayev declares no conflict of interest. A.N. Maltseva declares no conflict of interest. S.I. Sazonova declares no conflict of interest.

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Author Information Form

Popov Evgeniy V., resident at Nuclear department of Cardiology Research Institute, Federal State Budgetary Scientific Institution "Tomsk National Research Medical Center of the Russian Academy of Sciences", Tomsk, Russian Federation; **ORCID** 0000-0003-0772-6042

Anashbaev Zhanat Zh., resident at Nuclear department of Cardiology Research Institute, Federal State Budgetary Scientific Institution "Tomsk National Research Medical Center of the Russian Academy of Sciences", Tomsk, Russian Federation; **ORCID** 0000-0003-3169-0326.

Maltseva Alina N., resident and laboratory researcher at Nuclear department of Cardiology Research Institute, Federal State Budgetary Scientific Institution "Tomsk National Research Medical Center of the Russian Academy of Sciences", Tomsk, Russian Federation; **ORCID** 0000-0002-1311-0378

Sazonova Svetlana I., PhD, leading researcher at Nuclear department of Cardiology Research Institute, Federal State Budgetary Scientific Institution "Tomsk National Research Medical Center of the Russian Academy of Sciences", Tomsk, Russian Federation; **ORCID** 0000-0003-2799-3260

Author Contribution Statement

PEV – data collection and interpretation, manuscript writing, editing, approval of the final version, fully responsible for the content

AZhZH – data collection and interpretation, manuscript writing, editing, approval of the final version, fully responsible for the content

MAN – data collection and interpretation, manuscript writing, editing, approval of the final version, fully responsible for the content

SSI – contribution to the concept and design of the study, manuscript writing, editing, approval of the final version, fully responsible for the content

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