

# Epicardial Adipose Tissue Role as a Marker of Higher Vulnerability in Patients with Coronary Artery Disease

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## ABSTRACT

**Background:** Epicardial adipose tissue (EAT) has been recently identified as a major player in the development of the atherosclerotic process. This study aimed to investigate the role of EAT as a marker associated with a higher vulnerability of atheromatous coronary plaques in patients with acute myocardial infarction (AMI) as compared to patients with stable angina.

**Material and methods:** This analysis enrolled a total of 89 patients, 47 with stable angina (SA) and 42 with AMI, who underwent echocardiographic investigations and epicardial fat measurement in 2D-parasternal long axis view. The study lot was divided as follows: Group 1 included patients with prior AMI, and Group 2 included patients with SA. **Results:** There were no significant differences between the two groups regarding cardiovascular risk factors, excepting smoking status, which was recorded more frequently in Group 1 as compared to Group 2 (36.17% vs. 11.63%,  $p = 0.02$ ). The mean epicardial fat diameter was  $9.12 \pm 2.28$  mm (95% CI: 8.45–9.79 mm) in Group 1 and  $6.30 \pm 2.03$  mm (95% CI: 5.675–6.93 mm) in Group 2, the difference being highly significant statistically ( $p < 0.0001$ ). The mean value of left ventricular ejection fraction was significantly lower in patients with AMI (Group 1 –  $47.60\% \pm 7.96$  vs. Group 2 –  $51.23\% \pm 9.05$ ,  $p = 0.04$ ). EAT thickness values showed a weak but significant positive correlation with the level of total cholesterol ( $r = -0.22$ ,  $p = 0.03$ ) and with the value of end-systolic left ventricle diameter ( $r = 0.33$ ,  $p = 0.001$ ). **Conclusions:** The increased thickness of EAT was associated with other serum- or image-based biomarkers of disease severity, such as the left ventricular ejection fraction, end-systolic diameter of the left ventricle, and total cholesterol. Our results indicate that EAT is significantly higher in patients with acute coronary syndrome, proving that EAT could serve as a marker of vulnerability in cardiovascular diseases.

**Keywords:** atheromatous plaque, epicardial fat, vulnerability marker, acute coronary syndrome

## INTRODUCTION

Epicardial adipose tissue (EAT) represents an active organ with a high metabolic activity, releasing various bioactive molecules in the local and systemic circulation. The fat deposits surrounding the heart represent a relevant repository of various biomolecules, such as adiponectin, resistin, and inflammatory cytokines, all being significantly involved in the development and progression of atherosclerosis.<sup>1</sup> This process is also related to an increased inflammatory response at the level of the coronary arteries, leading to plaque vulnerabilization and plaque rupture or erosion, and finally resulting in an acute coronary syndrome.

EAT has been significantly correlated to the risk of future cardiovascular diseases, also being associated with the frequency and severity of other diseases such as diabetes mellitus, renal failure, or various conditions characterized by an increased inflammatory status.<sup>2</sup> The amount of pericoronary epicardial fat was also associated with the presence of coronary plaques inside the coronary tree, in a significantly higher extent than other fat deposits such as periaortic or extracardiac fat.<sup>3</sup> At the same time, the association between EAT volume and the incidence of coronary artery disease (CAD) has been demonstrated by several studies that indicated a higher risk of cardiovascular death in patients with larger EAT volumes.<sup>4</sup>

As a result of various studies that demonstrated a significant relationship between EAT and pro-inflammatory biomarkers, EAT is nowadays considered to represent a significant source of pro-inflammatory cytokines acting at systemic and local levels as well.<sup>5</sup>

While inflammation plays a significant role in the atherosclerotic process, there is no conclusive study yet to demonstrate the association between EAT and the vulnerability of coronary lesions in cardiovascular patients. A strong link has been demonstrated between increased EAT and major adverse cardiovascular event (MACE) rates in CAD patients, revealing the role of EAT as a predictor of cardiovascular events.<sup>6</sup> It has been shown that EAT increase is associated with an increased risk of developing plaque in the coronary arteries, indicating that EAT could be a new marker of vulnerability. Thus, an increased EAT could indicate the risk of an acute coronary event, perhaps through an inflammatory mechanism, because it is well documented that inflammation plays a significant role in platelet formation, progression, and rupture. EAT has been shown to be closely and directly related to the severity of coronary lesions, while being an independent risk factor for CAD,<sup>7</sup> even though the EAT volume did not provide relevant information on the functional significance of a coronary artery stenosis.<sup>8</sup>

Various imaging techniques have been proposed for the evaluation of EAT. The most useful and reliable one is computerized tomography (CT), a technique that allows accurate quantification not only of the EAT volume but also of the amount of pericoronary EAT, as well as the density determination of this tissue.

Despite the advantages offered by these top techniques, echocardiography remains an easily accessible method that can be used for routine examination of patients with CAD, including EAT assessment. In a recent study, an initial EAT value of over 7 mm was shown to be a significant predictor for MACE, death, revascularization, and myocardial infarction.<sup>9</sup> However, echocardiography can only determine the EAT diameter, while CT offers the benefit of more reliable quantification and, at the same time, an assessment of plaque vulnerability.

The aim of this study was to evaluate the role of EAT as a marker of vulnerability in establishing clinical cardiovascular prognosis in a group of patients diagnosed with stable angina (SA) and myocardial infarction (MI).

## MATERIAL AND METHODS

A total of 89 patients (47 with SA and 42 with MI) were enrolled to perform this assessment; all patients were admitted in the Cardio Med Medical Center in Tîrgu Mureş, Romania.

All patients underwent echocardiographic investigations using a Philips Sonos 7500 echocardiograph (Eindhoven, Netherlands), which included the determination of EAT thickness (EATT), left ventricular end-diastolic (EDLVD) and end-systolic (ESLVD) diameters, and left ventricular ejection fraction (LVEF). In addition, demographic data, medical history, routine biochemistry results, cardiovascular antecedents, and risk factors were also recorded upon admission.

The patients were divided into two groups, as follows: Group 1 comprised patients with non-anterior MI (lower MI, posterior IM, VDD) and anterior MI (antero-lateral MI, anteroseptal IM, lateral MI) and Group 2 comprised patients with SA.

The study was approved by the Ethics Committee of the institution, and all patients agreed with the investigations and signed an informed consent form. All study procedures were conducted in accordance with the World Medical Association's Declaration of Helsinki code of ethics.

Statistical analysis of the collected data was performed using the GraphPad Prim 3.1 software (GraphPad Software, Inc., San Diego, USA). Continuous variables are presented as mean  $\pm$  standard deviation, while categorical

**TABLE 1.** Patient baseline characteristics and cardiovascular risk factors

	Total (n = 89)	Group 1 (n = 47)	Group 2 (n = 42)	p value
	<b>Mean ± SD (95%CI)</b>			
Age (years)	63.49 ± 11.37 (61.11–65.87)	61.83 ± 11.60 (58.42–65.23)	65.30 ± 10.96 (61.93–68.67)	0.71
Male gender (n, %)	59 (66.29%)	35 (74.46%)	24 (57.14%)	0.08
Hypertension (n, %)	63 (70.78%)	28 (68.09%)	35 (83.72%)	0.13
Dyslipidemia (n, %)	21 (23.59%)	15 (31.91%)	6 (13.95%)	0.07
Smoking status * (n, %)	22 (24.71%)	17 (36.17%)	5 (11.63%)	0.02
Diabetes mellitus (n, %)	35(39.32%)	17 (36.17%)	18 (41.86%)	0.58
History of atherosclerosis (n, %)	25 (46.06%)	10 (21.28%)	15 (34.88%)	0.15

\* Past or present

variables are expressed as numbers and percent values (%). Student's t test was used for normally distributed continuous variables and the Mann-Whitney test for non-normally distributed continuous variables. Logistic regression analysis was performed in order to investigate the association between EATT and echocardiographic parameters. All statistical tests were two-sided, and a p value lower than the threshold  $\alpha = 0.05$  was considered statistically significant.

## RESULTS

A total of 89 patients were included in the study, of which n = 47 (52.80%) presented stable angina (Group 2) and n = 42 (47.20%) presented MI (Group 1). The patients' baseline characteristics, cardiovascular risk factors assessment, and the differences between the two groups are summarized in Table 1. The male population was larger in patients presenting MI: 74.46% of cases in Group 1 and 57.14% of patients from Group 2, though the difference was not statistically significant (p = 0.08). There were no significant differences between the two groups regarding history of

atherosclerosis (p = 0.15), hypertension (p = 0.13), diabetes mellitus (p = 0.58), dyslipidemia (p = 0.07), excepting smoking status, in Group 1 smoking being more frequent than in Group 2 (36.17% vs. 11.63%, p = 0.02).

The biochemical laboratory data analysis of the two groups showed that patients from Group 1 had significantly greater values than patients from Group 2 for the following biochemical parameters: hematocrit (43.13% ± 4.69 vs. 40.48% ± 4.564, p = 0.004), total cholesterol (202.5 ± 36.78 mg/dL vs. 175.9 ± 48.80 mg/dL, p = 0.003), liver enzymes ASAT (185.6 ± 156.0 U/L vs. 34.14 ± 32.06 U/L, p < 0.0001) and ALAT (52.30 ± 26.46 U/L vs. 29.68 ± 17.97 U/L, p < 0.0001) (Table 2).

The main echocardiographic structural and functional parameters according to group diagnosis classification are presented in Table 3. There were no significant differences between the two studied groups in terms of clinical characteristics such as NYHA class (p = 1.00), presence of tricuspid insufficiency (p = 0.48), mitral insufficiency (0.73), aortic insufficiency (p = 0.45), and pulse rate (p = 0.31) (Table 3).

**TABLE 2.** Biochemical laboratory data characteristics of the two groups

	Total (n = 89)	Group 1 (n = 47)	Group 2 (n = 42)	p value
	<b>Mean ± SD (95%CI)</b>			
Hematocrit (%)	41.86 ± 4.79 (40.86–42.87)	43.13 ± 4.69 (41.75–44.51)	40.48 ± 4.56 (39.07–41.88)	0.004
Triglycerides (mg/dL)	159.4 ± 76.63 (143.3–175.4)	167.0 ± 93.83 (139.5–194.6)	151.0 ± 51.61 (135.1–166.9)	0.75
Total cholesterol (mg/dL)	189.8 ± 44.74 (180.4–199.2)	202.5 ± 36.78 (191.7–213.3)	175.9 ± 48.80 (160.9–198.0)	0.003
Glycemia (mg/dL)	150.5 ± 93.02 (130.9–170.0)	156.0 ± 81.51 (131.8–180.2)	144.5 ± 104.6 (112.3–176.7)	0.10
Creatinine (mg/dL)	1.12 ± 0.52 (1.0–1.23)	1.04 ± 0.45 (0.91–1.17)	1.20 ± 0.59 (1.02–1.38)	0.06
Urea (mg/dL)	44.61 ± 26.88 (38.98–50.24)	43.57 ± 24.97 (36.24–50.90)	45.75 ± 29.09 (36.80–54.70)	0.75
Uric acid (mg/dL)	5.73 ± 1.93 (5.33–6.14)	5.56 ± 2.12 (4.93–6.18)	5.93 ± 1.70 (5.40–6.45)	0.15
ASAT (U/L)	114.1 ± 137.8 (85.08–143.1)	185.6 ± 156.0 (139.7–231.4)	34.14 ± 32.06 (24.15–44.13)	< 0.0001
ALAT (U/L)	41.49 ± 25.36 (36.18–46.81)	52.30 ± 26.46 (44.53–60.07)	29.68 ± 17.97 (24.15–35.21)	< 0.0001

**TABLE 3.** Clinical and echocardiographic characteristics

	Total (n = 89)	Group 1 (n = 47)	Group 2 (n = 42)	p value
		<b>Mean ± SD (95%CI)</b>		
MI type, anterior (n,%)	17 (19.10%)	8 (17.02%)	–	ns
MI type, non-anterior (n,%)		9 (19.14%)	–	
NYHA class 0	20 (22.47%)	10 (21.28%)	10 (23.26%)	1.00
NYHA class > II	67 (75.28%)	37 (78.72%)	30 (70.21%)	
Tricuspid insufficiency (n,%)	65 (73.03%)	33 (70.21%)	32 (76.74%)	0.48
Mitral insufficiency (n,%)	9 (10.11%)	4 (8.51%)	5 (11.63%)	0.73
Aortic insufficiency (n,%)	58 (65.16%)	32 (68.09%)	26 (60.47%)	0.45
Puls rate (bpm)	71.33 ± 8.99 (69.42–73.25)	72.26 ± 8.085 (69.88–74.63)	70.25 ± 9.948 (67.07–73.43)	0.31
LVEF (%)	49.33 ± 8.64 (47.52–51.14)	47.60 ± 7.96 (45.26–49.93)	51.23 ± 9.05 (48.45–54.02)	0.04
ESLVD (mm)	54.23 ± 5.99 (52.98–55.49)	39.32 ± 6.96 (37.28–41.36)	36.40 ± 7.15 (34.18–38.60)	0.05
EDLVD (mm)	37.92 ± 7.16 (36.42–39.42)	54.79 ± 5.52 (53.17–56.41)	53.63 ± 6.48 (51.63–55.62)	0.18
DsT (ms)	234.1 ± 63.21 (220.8–247.3)	239.6 ± 69.55 (219.2–260.0)	228.0 ± 55.64 (210.9–245.1)	0.6
Epicardial fat tissue diameter (mm)	7.77 ± 2.58 (7.23–8.31)	9.12 ± 2.28 (8.45–9.79)	6.30 ± 2.03 (5.675–6.93)	< 0.0001
Systolic blood pressure (mmHg)	127.8 ± 12.80 (123.4–132.3)	128.9 ± 14.40 (121.5–136.3)	126.8 ± 11.31 (120.9–132.6)	0.02
Diastolic blood pressure (mmHg)	74.24 ± 11.25 (70.25–78.23)	76.56 ± 14.32 (68.93–84.20)	72.06 ± 7.08 (68.42–75.70)	0.40

LVEF – left ventricle ejection fraction; ESLVD – end-systolic left ventricle diameter; EDLVD – end-diastolic left ventricle diameter; DsT – deceleration time

The mean epicardial fat diameter was  $9.12 \pm 2.28$  mm (95% CI: 8.45–9.79 mm) for Group 1 and  $6.30 \pm 2.03$  mm (95% CI: 5.675–6.93 mm) for Group 2, the difference being highly statistically significant ( $p < 0.0001$ ) (Figure 1). The mean value of LVEF measured by echocardiography was significantly lower in patients presenting MI (Group 1 –  $47.60\% \pm 7.96$  vs. Group 2 –  $51.23\% \pm 9.05$ ,  $p = 0.04$ ) (Figure 2).

The analysis of structural echocardiographic parameters showed no statistically significant differences between the

two groups in regard to the ESLVD ( $p = 0.05$ ), EDLVD ( $p = 0.18$ ), and deceleration time ( $p = 0.6$ ) (Figure 2).

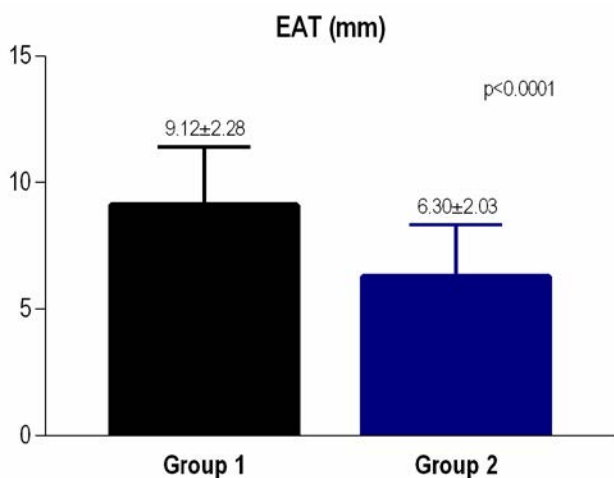
EATT values showed a weak but significant positive correlation with the level of total cholesterol ( $r = -0.22$ ,  $p = 0.03$ ) (Figure 3) and with the value of ESLVD ( $r = 0.33$ ,  $p = 0.001$ ) (Figure 4).

The simple linear regression analysis demonstrated that the EAT volume was negatively correlated with the level of LVEF ( $r = -0.34$ ,  $p = 0.0009$ ) (Figure 5).

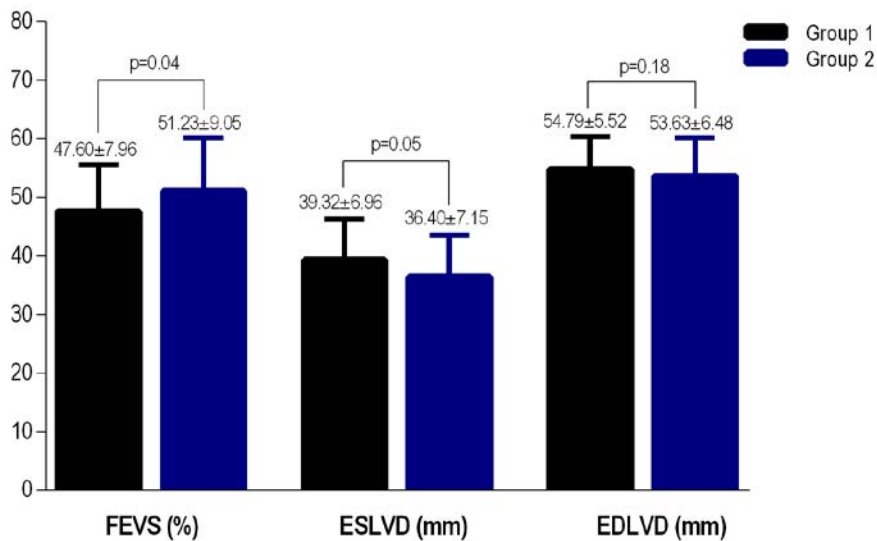
## DISCUSSION

In recent years, several studies have investigated a potential correlation between EAT and coronary artery plaque load, represented by different biomarkers, considering the biochemical properties of EAT and its role as a possible cardiovascular risk and vulnerability factor.<sup>10</sup> An estimate of EAT volume would be important, so several methods have been applied as a surrogate for its assessment. The noninvasive quantitative assessment of EAT volume on CT is feasible and could play an important role in assessing cardiovascular risk and vulnerability. Its correlation with the presence of CAD, severity, and prognosis have been demonstrated in various studies.<sup>11</sup>

EAT has been shown to be related to the presence and severity of coronary atherosclerotic lesions.<sup>12,13</sup> Studies revealed that subjects with an increased EAT value evaluated either by CT or cardiac echocardiography exhibit a more



**FIGURE 1.** Epicardial adipose tissue diameter in the two studied groups



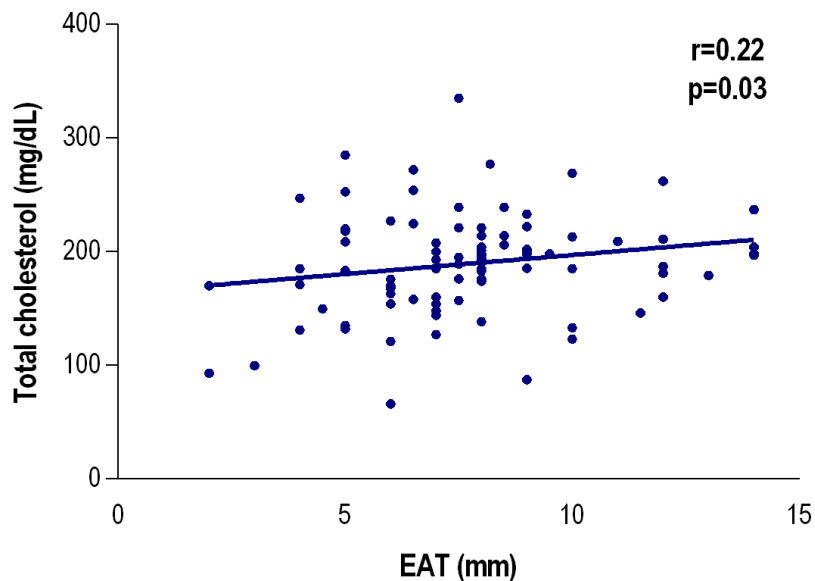
**FIGURE 2.** Comparison between structural echocardiographic parameters of the study groups

severe extension of coronary atherosclerosis, and EAT is also related to total plaque load and cardiovascular risk factors,<sup>14-16</sup> results confirmed by the present study where patients with MI showed significantly higher volumes of total cholesterol and presented dyslipidemia more frequently than patients with stable angina.

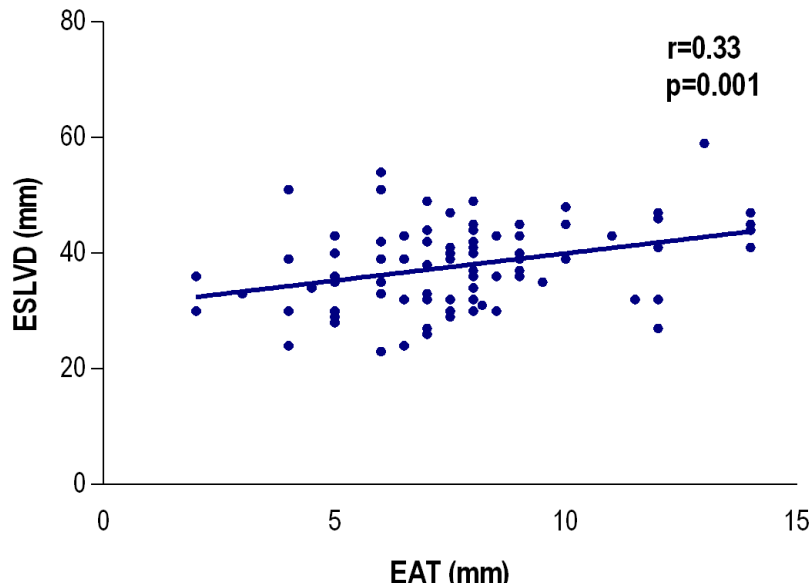
In addition, the incidence of MI appears to be directly proportional to the increase in epicardial fat, which is also related to a higher rate of MACE in subjects with known CAD.<sup>11,17,18</sup>

Furthermore, it has been shown that the thickness of epicardial fat is closely linked to the presence of multi-vascular CAD in patients with acute myocardial infarction.<sup>19</sup>

Wang *et al.* showed that there was a significantly higher rate of MACE during hospitalization for AMI in patients with an EAT thickness of >4.7 mm ( $p = 0.02$ ) after multivariate adjustments.<sup>20</sup> Another study of the prognostic value of EAT in STEMI compared with NSTEMI showed that an average 2.6 mm of EAT had a significant predictive



**FIGURE 3.** Correlation between the thickness of the epicardial adipose tissue and the levels of total cholesterol



**FIGURE 4.** Correlation between the thickness of the epicardial adipose tissue and the diameter of end-systolic left ventricle

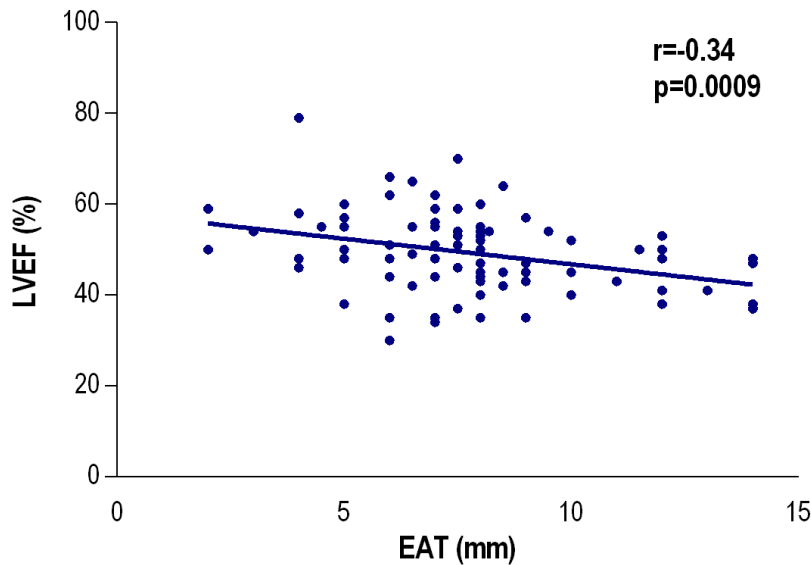
capacity for the primary endpoint of both univariate and multivariate regression.<sup>21</sup>

Tanindi *et al.* showed that patients with AMI had a significantly higher EAT compared to unstable angina or stable CAD patients ( $p < 0.001$ ). Similarly, the present investigation revealed that patients from Group 1, presenting MI, had significantly higher EAT values than patients from Group 2, diagnosed with stable angina ( $p < 0.0001$ ).<sup>22</sup>

Also, epicardial fat was associated with an increase in systemic inflammatory status in patients with type 2 dia-

betes mellitus with AMI, and a higher EAT thickness was associated with an improved left ventricular remodeling process and a lower ejection fraction at six months.<sup>23</sup> Also, Tanindi *et al.* demonstrated that EAT thickness measured by echocardiography is independently associated with MI.<sup>24</sup>

Epicardial fat could provide additional evidence of future cardiac events in patients with acute coronary syndromes (ACS). It is well known that an increase in systemic inflammatory status leads to a lower prognosis in



**FIGURE 5.** Correlation between the thickness of the epicardial adipose tissue and LVEF

patients with STEMI.<sup>25,26</sup> As an active metabolic tissue that secretes inflammatory cytokines and chemokines, epicardial fat may contribute to global inflammation, adversely affecting the outcome and prognosis of patients with ACS. EAT thickness can be used as a predictor of MACE, including MI and sudden death.<sup>24</sup> In addition, it has been shown that an increased volume of epicardial adipose tissue predicted MI or cardiovascular death in patients suspected of CAD.<sup>27</sup>

## CONCLUSIONS

In conclusion, there is a relationship between EATT and coronary atherosclerotic burden in CAD patients. The increased thickness of EAT was associated with other biomarkers of disease severity such as LVEF, ESLVD, and total cholesterol. Therefore, the EAT volume could represent a new imaging-derived biomarker, useful to characterize the severity of CAD. Information provided by EAT can be used as a predictor of MACE in patients with ACS, both in the short and long term. Our results indicate that EAT is significantly higher in patients with ACS; thus, we can state that EAT could play a role of marker of vulnerability in establishing cardiovascular prognosis.

## CONFLICT OF INTEREST

None to declare.

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